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Japan Report

SCIENCE AND TECHNOLOGY

SPECIAL NOTICE INSIDE

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JPRS-JST-87-017

26 MAY 1987

JAPAN REPORT

SCIENCE AND TECHNOLOGY

CONTENTS

AEROSPACE SCIENCES

National Aerospace Laboratory News Updated
(KOGIKEN NYUSU, Feb 87) 1

Composite Airfoil FOD Tester 1
Peripheral-Scanning Geostationary Satellite,
by Hajime Koshiishi 3
RSS^2 Flight Control System 5
CAD-Designed STOL Model Tested 8
Life-Support Technology 13

BIOTECHNOLOGY

Applications of Immobilized Enzymes Discussed
(BIOINDUSTRY, Dec 86) 16

Computer Aided Protein Design (CAPD) Discussed
(Haruki Nakamura; BIOINDUSTRY, Nov 86) 29

LASER TECHNOLOGY

Application of Lasers in Chemical Industry Discussed
(Akira Yabe; OPTRONICS, Oct 86) 42

NEW MATERIALS

Future of New Glass Industry Examined
(NIKKO MATERIALS, Dec 86) 52

/9987

NATIONAL AEROSPACE LABORATORY NEWS UPDATED

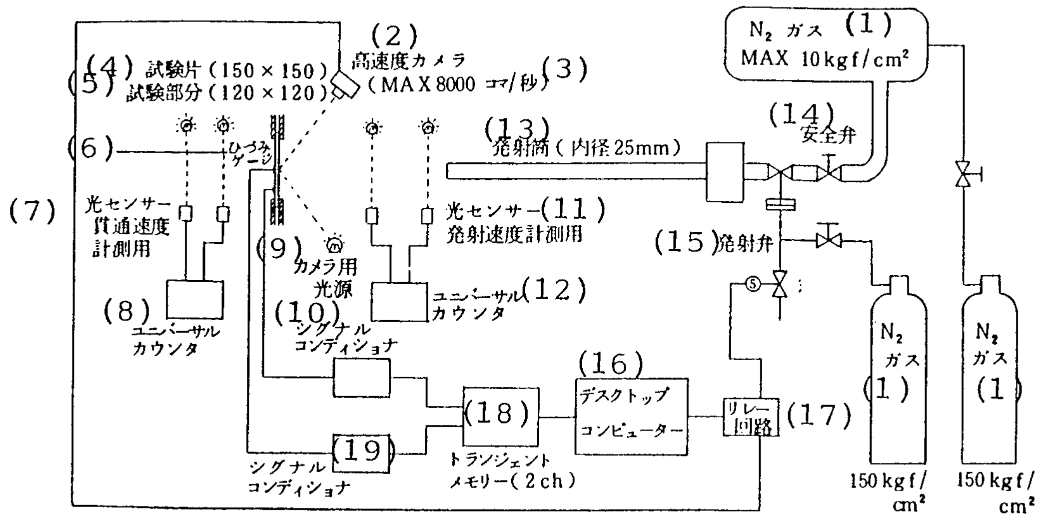
Composite Airfoil FOD Tester

Tokyo KOGIKEN NYUSU in Japanese Feb 87 pp 3-5

[Article by Motor Structure Research Room]

[Text] The use of carbon-fiber reinforced FRP (fiber reinforced plastic) in the fan blades of aircraft engines was tested by the British in 1960, but practical implementations were never achieved due to inadequate FOD (foreign object damage) resistance. Since then, the evaluation and improvement of FOD resistance has been a major theme of composite materials research. At the National Aerospace Laboratory (NAL), the FOD test unit depicted in the block diagram in Figure 1 is being set up and adjusted to evaluate the FOD resistance of composite airfoils for the ATP (advanced turboprop), etc. This FOD tester has the following features. 1) The gas firing system in which high-pressure nitrogen gas is used allows for better control of the firing speed than do explosive systems. In the experiments, firings were possible through a wide speed range of 40 - 500 m/s. 2) No projectile enclosure (sabot) is used, so it can be shot into the target with great precision, although, on the other hand, the diameter of the projectile cannot be changed. 3) It is not necessary to clean the unit after each firing, making it convenient to use. Projectile speed measurement is implemented with a custom photosensor system that combines operating amplifiers with highly responsive photodiodes, assuming a maximum firing speed of 500 m/s for a 25-mm long object. Impact strain was monitored by recording in transient memory, via a signal conditioner (maximum response frequency = 200 kHz), the output of strain guages attached to the test pieces in two locations. The transient memory is a two-channel device having a capacity of 64 kilowords (1 word = 12 bytes) per channel. It can record 0.6 seconds of data for 100 kHz sampling. The experiments were done on high-speed phenomena which could be finished in a short time, so the control and analyses involved in the firing of the projectile and making subsequent measurements were done with a desktop computer. A 16mm camera is scheduled to be used for high-speed photography (maximum 8000 frames/second) to monitor the modes of change in the test pieces, observe the destruction process, and verify the projectile velocity. The test pieces are panels that measure 150 x 150 mm, with the test area becoming 120 x 120 mm after the panels are fixed into supporting jig frames. The projectiles impact the test pieces perpendicularly.

Figure 1 Block Diagram of FOD Tester



Key:
1. N2 gas
2. High-speed camera
3. (MAX 8000 frames/second)
4. Test piece (150 x 150)
5. Test area (120 x 120)
6. Strain guage
7. Photosensors for measuring penetration velocity
8. Universal counter
9. Light source for camera
10. Signal conditioner
11. Photosensors for measuring firing velocity
12. Universal counter
13. Firing tube (internal diameter = 25 mm)
14. Safety valve
15. Firing valve
16. Desktop computer
17. Relay circuitry
18. Transient memory (2 ch)
19. Signal conditioner

We will now report briefly on the results of the preliminary tests done on the metal (titanium alloy (thickness 0.7 mm), aluminum alloy (thickness 1 mm)) and FRP (CF epoxy cloth material (thickness 2 mm)) panels using this test apparatus. In cases where the velocity is below the threshold penetration velocity, fiber severing and peeling is observed in the CF epoxy material in the vicinity of impact, but there is little externally visible change, whereas with the aluminum alloy, dents occur in the impact area, depending on the impact velocity, and overall plastic deformation is observed. In cases where the velocity is around the threshold velocity of penetration, cracks and large broken pieces are produced in the CF epoxy material, being the worst of all three cases (i.e. below, at, and above impact velocity). With the aluminum alloy, holes occur which open up like flower petals, and the plastic deformation reaches maximum. In cases where the velocity is above the threshold penetration velocity, with the CF epoxy material, holes open that have the same diameter as the projectile, with damage being limited to the immediate vicinity of the hole. With aluminum alloy, plugs occur. With all of the test pieces, the greater the impact velocity becomes, the more the damage is limited to the vicinity of the hole. When FOD resistance is evaluated at the threshold penetration velocity, CF epoxy is found to be weaker than the titanium or aluminum alloys. We believe that the FOD resistance of composite materials can be sharply improved, however, by the appropriate selection of fibers and of matrix and lamination conditions. There are now plans for going ahead with experiments on the effects of material quality and lamination methods, through which more basic information will be collected on evaluating the FOD-resistant characteristics of composite airfoils.

Peripheral-Scanning Geostationary Satellite

Tokyo KOGIKEN NYUSU in Japanese Feb 87 pp 5-7

[Article by Hajime Koshiishi, Measurement Department]

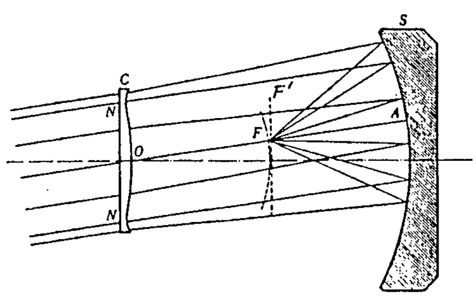
[Text] Earth monitoring is best done by continuous observations from geostationary satellites. We here propose a concept for an earth monitoring satellite that can make observations with a resolution of 100 m from stationary orbit. The basic specifications of this concept are as follows.

Position of Satellite: Stationary orbit, east longitude 124°C (approximate)
Distance from Japanese Archipelago: Average 38,000 km
Instantaneous Visual Range on Earth Surface: 100 m
Light receptor element: 14 µm x 14 µm photo diode
Observation wavelength: 0.5 µm - 1.0 µm
Light collection system (telescope) focal length: 5.35 m
Aperture of light collection system: 1 m

The size of the light receptor element noted above reflects the dimensions of one element of the photodiode arrays which are now generally available. From the sensitivity range of this element the observation wavelength is determined. The focal length, moreover, is determined from the distance of the stationary satellite from Japan, the instantaneous visual range on the earth's surface, and the size of the light receptor elements. An aperture of approximately 0.5 m is good enough if the observation wavelength is set at 1.0 µm and an analytical threshold resolution of 100 m is assumed, but this value becomes at least 1 m when consideration is given to the performance deterioration caused by the atmosphere.

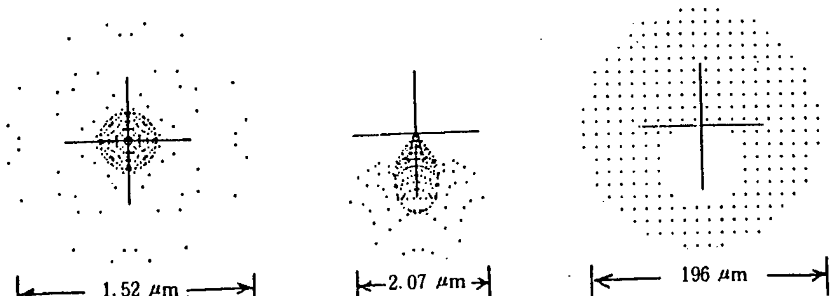
There are refracting telescopes, reflecting telescopes, and catadioptic (reflecting/refracting) telescopes. Refracting telescopes are configured with lenses, and give a wide-angle view, but suffer from chromatic aberration and high weight. Reflecting telescopes produce no chromatic aberration and can be made much lighter than refracting telescopes, but have a narrow angle of view. Catadioptic telescopes are susceptible to some color aberration, but can have a rather wide angle of view and are lightweight. Accordingly, the Schmidt system--a type of catadioptic system--is used in the telescopes carried on geostationary earth-monitoring satellites. Figure 1 diagrams the principle of the Schmidt telescope. S is the spherical main mirror. C is a spherical color-correcting lens. The light rays coming in diagonally constitute a vertical object with respect to the principal ray OA, and neither comatic aberration nor astigmatism occur. The focal length is OF, and the image plane F is spherical. On such a spherical image plane there is no spherical aberration, comatic aberration, or astigmatism, so an ideal image can be obtained. The circle in Figure 2 that contains the arc of the Japanese Archipelago is a projection of that image plane on the surface of the earth. By arranging light receptor elements along the circular arc on the image plane, ideal photoelectric conversion can be done, and ideal images obtained. This is called peripheral scanning. Figure 2 indicates the visual field obtained with a Schmidt telescope, in stationary orbit, having an aperture of 1 m and a focal length of 5.35 m (with an overall telescope length of approximately 11 m). The optical axis is within mainland China (the black dot in the figure). The Japanese Archipelago is on the periphery, with an angle of view of 1.65°C from the optical axis obtaining there.

Figure 1   Principle of Schmidt Telescope



A spherical-aberration correcting lens is a high-dimensional aspherical lens. A 4-dimensional aspherical surface is assumed here. The parameters that represent that surface were determined using the commonly used formulae for optically designing the Schmidt telescope. The spacial resolution analysis for the telescope was done using the general-purpose optical computational program ACCOS-V of Century Research Center, Ltd. In Figure 3 are given some of the spot diagrams that resulted. The diagram in (a) indicates what position on the image plane (F in Figure 1) the light energy that comes in along the optical axis of the telescope is focused on, from 100 m x 100 m picture elements on the earth. The diagram in (b) indicates the optical convergence of the light energy from 100 m x 100 m picture elements (such as the picture elements of the Japanese Archipelago in Figure 2) on the earth, coming in at an angle of 1.65° from the optical axis. The diagram in (c) indicates the optical convergence at an angle of vision of 1.65° on a flat plane tangential to the F' plane (i.e. the image plane) in Figure 1. From these spot diagrams it is learned that the optical convergence on the image plane, even at a visual angle of 1.65°, is adequately small compared to the size of the 14 μm x 14 μm light receptor elements. However, it also found that, in flat planes that are at a distance from the image plane (i.e. on the F' plane), there is rapid deterioration as the distance from the optical axis increases.

Figure 3 Image Plane (F Plane in Fig 1) and Flat Plane Tangential Therewith (Spot diagrams in F' plane in Fig 1)



(a) F Plane on axis (b) F Plane Half vis angle = 1.65° (c) F' Plane

As a result of the investigations discussed above, it is understood that the dream of conducting earth observations from geostationary orbit with a 100-m spatial resolution can be realized in practical systems by using Schmidt telescopes as the light-collecting system and employing peripheral scanning along the image plane.

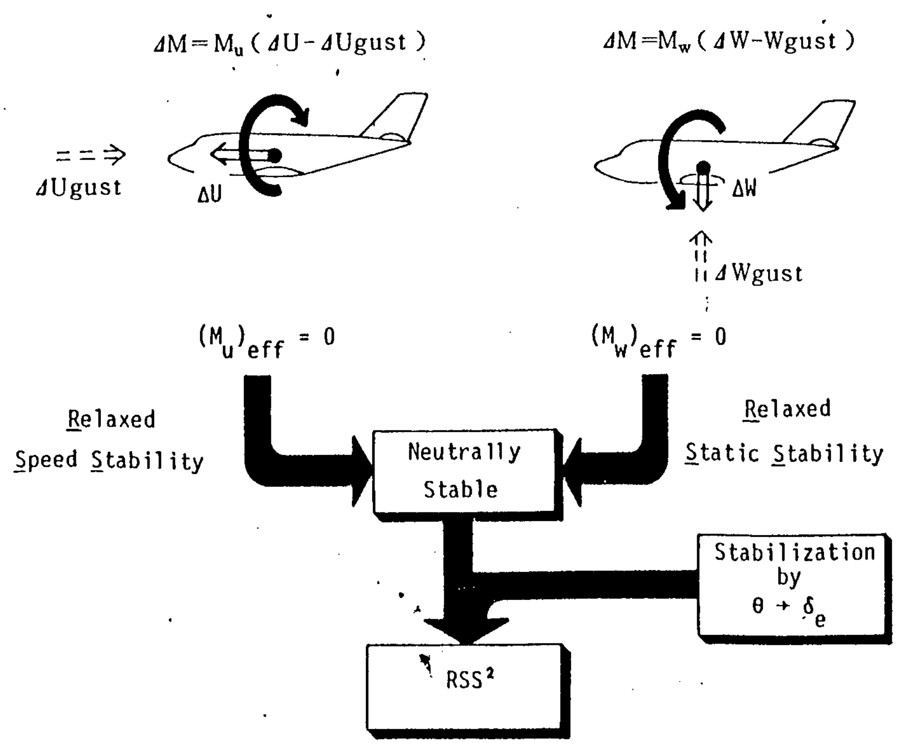
RSS² Flight Control System

Tokyo KOGIKEN NYUSU in Japanese Feb 87 pp 7-9

[Article by Flight Testing Department]

[Text] RSS (relaxed static stability) technology radically reduces the size of an aircraft's horizontal stabilizer, thereby effecting a weight reduction (due to the growth factor) that is many times greater than the actual portion of the reduction, and also reducing drag during flight. One of the main functions of the horizontal stabilizer is to naturally return the aircraft to a well-trimmed angle of attack when the angle of attack has been disrupted by disturbances such as vertical gusts. In other words, the horizontal stabilizer produces weathervaning stability in the vertical. This is called angle-of-attack static stability. Thus when the empennage

Figure 1 Principles of RSS^2 Flight Control System

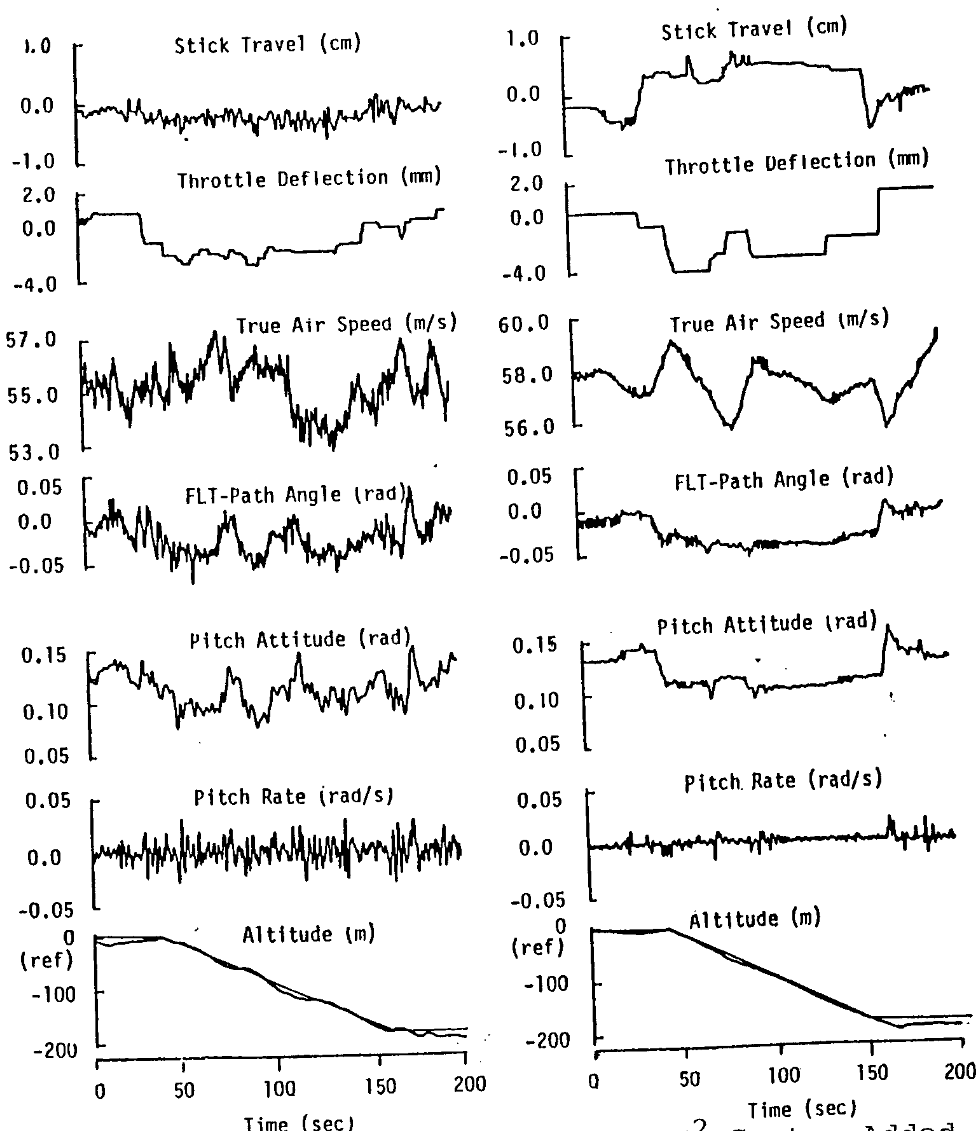


is designed small in keeping with RSS technology, the characteristic angle-of-attack static stability of the aircraft is lost, making it necessary to regain this stability by means of automatic flight controls. Two basic methods are used to effect automatic stabilization, i.e. (1) the method of recovering the same degree of angle-of-attack static stability as with an ordinary hoizontal stabilizer by taking angle-of-attack or vertical acceleration signals and feeding them back to the elevators, and (2) the method of maintaining the pitch attitude angle of the airframe relative to the earth by feeding back gyroscope signals to the elevators.

In general, method (1) has been given the most attention, but by using method (2) to effect stability, it is possible to elicit other advantages besides the weight and drag reductions that are possible with RSS technology. Specifically, since attitude stabilization is effected with small angle-of-attack static stability, the aircraft becomes like a log with respect to vertical gust disturbances, so that airframe rolling and pitching become extremely small and riding comfort is markedly improved. This fact is very little appreciated in this country. With stabilization method (2), moreover, attitude maintenance itself--a fundamental pilot control operation--is automated, and the ease of aircraft control is dramatically improved. When this point is fully appreciated, it is possible to enjoy the same advantages relative to vertical gusts as the small-empennage RSS aircraft in ordinary airframes that have undiminished horizontal stabilizers by, conversely, feeding the angle of attack back to the elevators, thereby substantially eliminating angle-of-attack static stability, and instead effecting attitude stabilization by method (2).

The airframe attitude of an aircraft also changes with viscitudes in airspeed caused by horizontal gusts. This is called speed stability. In aircraft which exhibit extremely strong speed stability due to the power effect, pitch attitude disturbances are believed to intensify at low altitudes where horizontal gusts are predominately found. Cognizant of these

Figure 2 RSS² Effectiveness



Unmodified Acft (B-65)

RSS² System Added

things, we experimented with feeding back the airspeed to the elevators to relax the speed stability, so that the airframe pitch attitude would not vary with speed changes either. We then proposed a new RSS² flight control system (at the 1983 Aircraft Symposium) in which both relaxed (angle-of-attack) static stability and relaxed speed stability are rigorously implemented, and method (2) of auto-stabilization is employed for attitude maintenance. The principles of this RSS² are diagrammed in Figure 1.

We loaded the RSS² flight control rules discussed above into a computer carried aboard NAL's experiment-support aircraft VSRA and conducted system evaluations with actual flight tests. Some of the flight test data is given in Figure 2. The plots in the lefthand column indicate time responses in model landing experiments at high altitude with the unmodified aircraft, while the plots in the righthand column are from the experiments done with the addition of the RSS² control system in the same aircraft. The plots on the left and right are drawn to the same scale in the interest of making comparisons on the vertical coordinates. It is clear that the control stick movements became smoother with the addition of the RSS², with forward stick pressure being used as the aircraft decended, and the pitch attitude following this, as can be seen. In particular, the difference in pitch rate (i.e. speed of change in attitude) is large, indicating that, when RSS² control was employed, there was almost no attitude change due to disturbances. Thus it was confirmed that the good results aimed at were achieved.

The RSS² flight control rules achieve the characteristics of an extreme system having unlimited gain, in high gain theta-closure (well known to specialists in the field), with multiple loops of limited gain.

CAD-Designed STOL Model Tested

Tokyo KOGIKEN NYUSU in Japanese Feb 87 pp 9-11

[Article by New Aircraft Research Group: "Wind-Tunnel Tests on Half-Scale STOL Model Designed With CAD (Second Report)"]

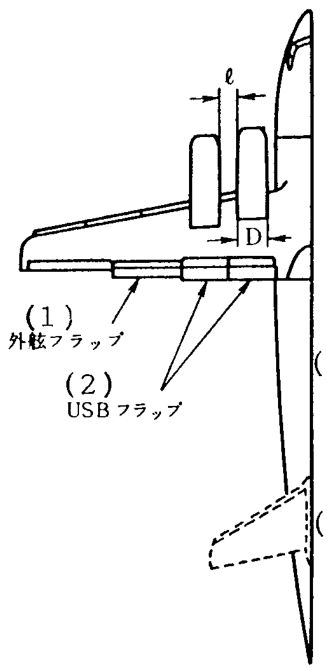
[Text] The initial tests on this model were conducted last year, primarily to determine the aerodynamic characteristics of the main wing configuration. Since the second battery of tests was made this hear, the focus has been on obtaining the necessary aerodynamic data that are necessary in order to determine the effectiveness of the various aerodynamic elements and ascertain methods of improvement, in the interest of achieving the most optimal aerodynamic forms for the USB-type STOL craft.

The main objectives in this round of tests are 1) to ascertain the changes in aerodynamic characteristics resulting from partial improvements in the model such as modification of the outboard flap hardware and improvements in the USB nozzles subsequent to the initial tests, 2) to ascertain the effects of engine position, which is a critical element in the USB design, particularly with regard to the effects on the aerodynamic characteristics between the two engines mounted on the upper surface of the main wings, and 3) to determine the effects of the leading-edge slots which constitute one of the mechanical high-lift systems.

With respect to testing methods, besides making force measurements with ordinary six-component balances, a slip-stream measuring device based on an experimental comb-shaped five-hole tube was also used, engine exhaust flow behind the main wings was measured as part of objective 2), and observations of flows above the airfoils were made, based on the air-flow system. The results of these tests are now being analyzed, but we can report here on some of the results gained thus far.

Engine-interval tests were conducted in one case with the interval about the same as in the experimental STOL aircraft "Hicho" that is now undergoing flight tests, and in two other cases with wider intervals (cf. Figure 1). In each case, moreover, tests were done with two types of flaps having different widths.

Figure 1 Comparison of Major Specifications for Main Wing of CAD Half-Size Model



(3) 面積（片翼，m²）	0.2997
(4) 翼幅（片翼，m）	1.224
(5) アスペクト比	10.0
(6) 平均空力翼弦長（m）	0.2637
(7) 後退角（deg）	8.2
(8) テーパー比	0.35
(9) 翼厚比（%）	(12) 15（翼根），12（平均）
(10) USBフラップ	(13) ダブル・フラップ
(11) 外舷フラップ	(14) 2重隙間フラップ

(15) 注1.エンジン間隔S（＝ℓ/D）は外エンジンを移動させる事によりS＝0.31，0.54及び0.77と変化させた。この時，ボルテックス・ジェネレータもそれに対応して移動させた。

(16) 注2.USBフラップ・スパンは外側のUSBフラップ・スパンを短の場合185 mm，長の場合240 mmとした。

Key:
1. Outboard flap
2. USB flaps
3. Area (one wing, m^2)

4. Wingspan (one wing, m)
5. Aspect ratio
6. Mean length of aerodynamic wing chord (m)
7. Angle of sweepback (deg)
8. Taper ratio
9. Wing thickness ratio (%)
10. USB flaps
11. Outboard flap
12. 15 (wing root), 12 (average)
13. Double flap
14. Double-slotted flap
15. Note 1: The engine interval S (= el/D) was changed between S = 0.31, 0.54, and 0.77 by moving the outboard engine. The vortex generator was also moved accordingly.
16. Note 2: The USB flapspan was made 185 mm with the shorter outboard USB flap, and 240 mm with the longer outboard USB flap.

In Figure 2 are given single examples of the static thrust characteristics (i.e. the deflection characteristics for engine thrust (exhaust flow) with wind-tunnel windspeed at zero) for the main-wing aerodynamic form in the cruise (C/N), takeoff (T/O) and landing (L/D) configurations. In Figure 3, the coefficient of lift C_L, coefficient of drag C_D, and coefficient of pitching moment C_M for engine interval S (cf. Figure 1) and angle of attack alpha = 0° are plotted, based on the results of vertical three-component measurements made in blower tests. With the static thrust characteristics (Figure 2) for the cruise configuration (USB flap angle δ_{fusB} = 0°), there are no clearcut differences in the characteristics even when S is changed, but as δ_{fusB} becomes larger, moving from the takeoff to the landing configurations, differences develop in the thrust deflection angle δ_j with changes in S. In particular, d_j is about 2.5° - 5° smaller in the case where the engine interval S is widest at 0.77 than in the cases were the interval is narrower. With the three-component characteristics of Figure 3, the characteristics change according to S with conditions other than C_J = 0 (results for cruise configuration are not shown, but there was almost no change in the three-component characteristics with changes in S). In particular, when there are changes in the values of C_L and C_D with changing S in the same configuration, C_D is found to increase (or decrease) when C_L increases (or decreases). After examining the quantitative changes in these two values, it is reasonable to assume that they are dependent on changes in δ_j due to changing S. Concerning the changes in C_M, moreover, it can be inferred that the higher the value of δ_j becomes, the closer the engine exhaust flow will be fixed to the trailing edge of the USB flaps, and that the center of wind pressure will move aft, resulting in a nosedown moment (i.e. negative C_M). As a result, it was confirmed that finding the optimum engine interval is a critical question for powered lift, and that a value of S in the neighborhood of 0.54 is the best engine interval for the USB nozzle shape in this model.

Figure 2   Static Thrust Characteristics

	(1) 主翼空力形態	(2) USB フラップ角	(3) 外舷 フラップ角	(4) 前縁 スラット角	(5) エルロン 舵角
(6)	巡航 (C/N)	0°	0°	0°	0°
(7)	離陸 (T/O)	30°	30°	20°	0°
(8)	着陸 (L/D)	50°	50°	40°	0°

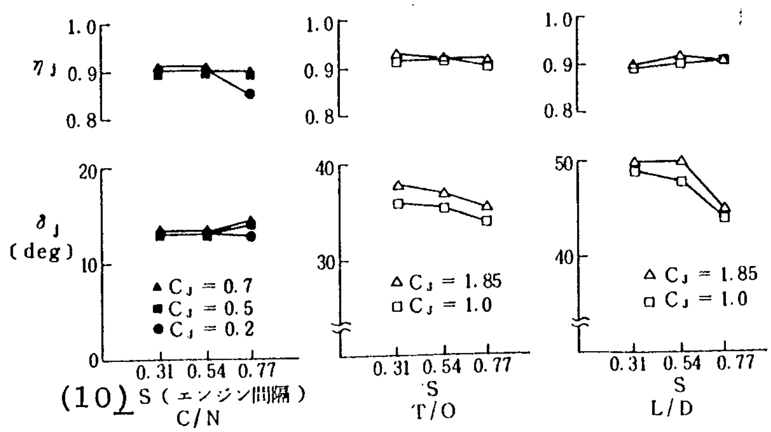
(9) 各形態ともボルテックス・ジェネレータ付

(11) δ_J (推力偏向角) = $\tan^{-1}$ (T_N/T_A)
但しT_A, T_Nは各空力形態でのエンジン推力の水平方向成分と垂直方向成分である。

(12) η_J (推力偏向効率) = $\sqrt{T_N^2 + T_A^2}/T_T$
但しT_Tはエンジン後方に主翼後縁板やUSBフラップがない時の同回転数での推力

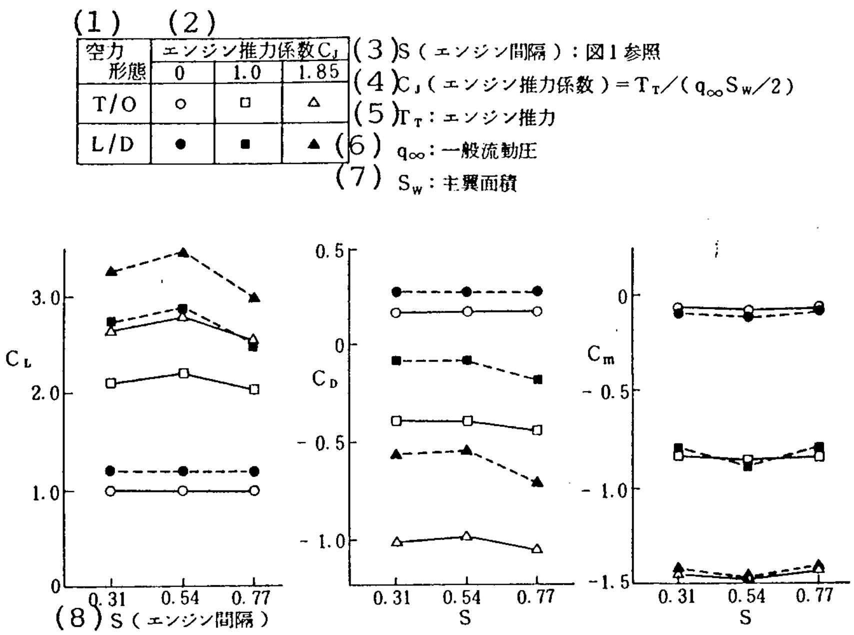
(13) C_J はエンジン推力の大きさを相当するエンジン推力係数 (図3参照) で表わしたもの

(14) S (エンジン間隔) = ℓ/D (図1参照)



Key:
1. Main-wing aerodynamic configuration
2. USB flap angle
3. Outboard flap angle
4. Leading edge slot angle
5. Aileron deflection angle
6. Cruise (C/N)
7. Takeoff (T/O)
8. Landing (L/D)
9. Vortex generator used with each configuration
10. S (engine interval)
11. δ_j (thrust deflection angle) = $\tan^{-1}$ (T_N/T_A)
 where T_A and T_N are the horizontal and vertical components of engine thrust in each aerodynamic configuration
12. he$_j$ (thrust defflection efficiency) = $\sqrt{T_N 2 + T_A 2 / T_T}$
 where T_T is the thrust at the same rpm when there is no main-wing trailing-edge plate or USB flap aft of the engine(s)
13. C_J is the coefficient of engine thrust which corresponds to the size of engine thrust (cf. Figure 3)
14. S (engine interval) = el/D (cf. Figure 1)

Figure 3 Comparison of Vertical Three-Component Forces (alpha = 0°) According to E/G Interval

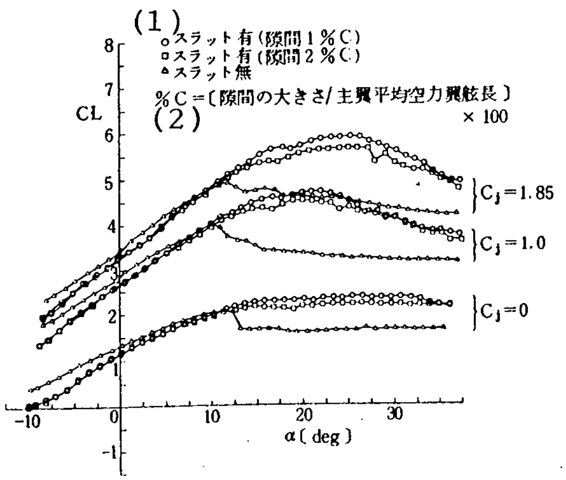


Key:
1. Aerodynamic configuration
2. Engine thrust coefficient C_J
3. S (engine interval) : Cf Figure 1
4. CC_J (engine thrust coefficient) = $T_T/(q_\infty/2)$
5. T_T : Engine thrust
6. q_∞ : General flow pressure
7. S_W : Main wing area
8. S (engine interval)

In Figure 4 are plotted the C_L - alpha characteristics with and without leading-edge slots. The leading-edge slots are effective in retarding the stalling of the outer wing (portion beyond outboard engine) and in increasing maximum lift, but in these tests, in the vicinity of low angle of attack, C_L was greater when there were no leading-edge slots. With respect to the gap between the slot and the leading edge of the main wing, moreover, it was better when the gap was a small 1 percent of C (cf. Figure 4). Together with the shape of the flow path, the size of this gap is important to the performance of the outboard (double-slotted) flap, and we now know that it is an item demanding thorough study.

We plan to issue a final and more detailed report on these tests, including the results noted above, as soon as the studies are completed.

Figure 4 C_L - alpha Curves (Landing Configuration, With Vortex Generators)



Key:
1. (circles) With slots (gap 1%C)
   (squares) With slots (gap 2%C)
   (triangles) Without slots
2. %C = (size of gap)/(mean aerodynamic chord length of main wing)

Life-Support Technology

Tokyo KOGIKEN NYUSU in Japanese Feb 87 pp 12-13

[Article by Space Research Group: "Research on Closed-Ecology Life-Support Technology"]

[Text] Japan is participating in the Space Station Project and is obliged to march in step with the United States in developing outer space. CELSS (closed-ecology life-support systems) is a technology that is crucial to man's conquest of space. The CELSS Research Society was formed and began conducting studies in this field 4 years ago.

A report entitled "CELSS Experiment Concepts of Space Station Mission" was issued by this society in April, 1984. With this report we were able to set forth the experimental projects necessary to perfect CELSS technology by the 21'st century. The report was warmly received both at home and abroad, and resulted in members of the society being invited to attend the 1985 SAE Conference and NASA's CELSS '85 Workshop. The society members who attended these functions were Oya Haruhiko (Yokohama National Univ), Akio Takahashi (Niigata Univ), Atsushi Ashida (Hitachi Limited), Shuji Kanda (Kawasaki Heavy Industries), and Keiji Niida (National Aerospace Laboratory). At the 1986 COSPAR Conference workshop "Bioregenerative Life Support Systems in Space," moreover, the society was asked to help form the organizational committee. With Niita handling the coordination, Japan was able to submit 10 papers, as listed in Table 1.

Table 1 Papers Submitted at COSPAR (1986)

Author	Title
Oguchi, Ohira, Niita (NAL)	Food Production and Gas Exchange System Using Blue-Green Algae
Oya, Matsumoto (Yokohama National Univ)	Gas Exchange Systems and Sunlight Supply System in Microalgal Bioreactor System
Otsuji (Mitsubishi Heav Ind) Kanda (Kawasaki Heavy Ind)	Preliminary Experimental Results of Gas Recycling Subsystem Except Carbon Dioxide Concentration
Ashida (Hitachi), Tsuji (Sasakura)	Vapor Compression Distiller and Membrane Technology on Water Revitalization
Nishi (Rika U), Niita (NAL)	Fundamental Study on Gas Monitoring in CELSS
Takahashi (Niigata U), Niita, Oguchi (NAL)	The Applicability of Catalytic Wet-Oxidation to CELSS
Mizuya (Mitsubishi Chem Ind)	A Large Scale Perspective on Eco-System
Niita (NAL)	An Overview of Japanese CELSS Research Activities
Takano (Meijo Univ)	Trickle Water and Feeding Systems in Plant Culture and Light-Dark Cycles Effects on Plant Growth
Taisei (Nat'l Environ Polution Research Institute)	Image Instrumentation for Extracting Plant Physiological Information

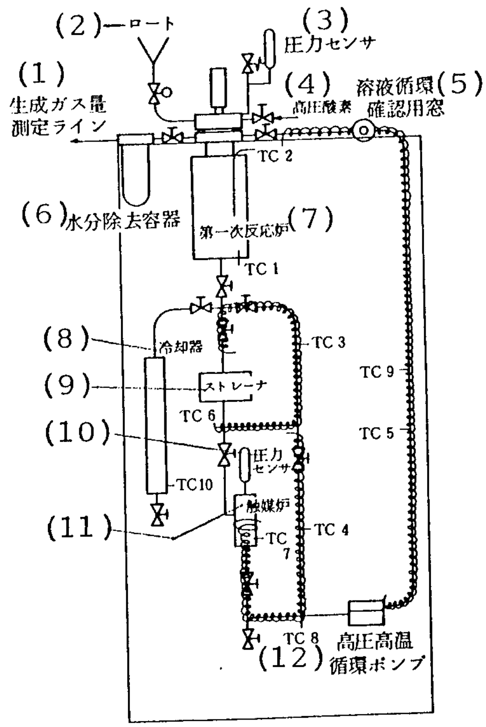
The papers submitted from Japan amounted to roughly half of the total, and Japan's reputation in this field seems to have risen considerably. Niita has been selected as a member of the executive committee for the workshop which will be held in Helsinki in 1988. This laboratory is conducting research in several CELSS-related fields, including gas circulating technology, water purification and circulating technology, waste decomposition technology, and technology for growing seaweed in order to convert carbon dioxide to oxygen. The laboratory also acts as overall coordinator to concentrate the activities of other organizations on CELSS research.

Basic experimentation in waste decomposition was recognized for Science and Technology Promotion Adjustment treatment in fiscal 1985 and 1986. In the first year, a high-temperature, high-pressure autoclave was used in conducting wet oxidation experiments.

The results of these experiments indicated the presence of ammonia, potassium, and phosphate ions in the residual liquid after wet oxidation, and suggested a high possibility of using this material for plant fertilizer, but problems were also identified, such as the precipitation of calcium salts in the residual liquid and the remaining of undiscomposed acetic acid. This pointed to the need for a catalyst in decomposing the acetic acid, and ruthenium was found to be an ideal catalyst for this purpose.

The equipment is now being modified so that wet oxidation can be performed in fiscal 1986 using catalysts. In Figure 1 is given a block diagram of the modified system now being prepared.

Figure 1 Simplified Diagram of Waste Processing System



Key:
1. Line for measuring quantity of gas generated
2. Load
3. Pressure sensor
4. High-pressure oxygen
5. Window for visual verification of solution circulation
6. Moisture elimination vat
7. Primary reactor
8. Cooler
9. Strainer
10. Pressure sensor
11. Catalytic reactor
12. High-pressure high-temperature circulation pump

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APPLICATIONS OF IMMOBILIZED ENZYMES DISCUSSED

Tokyo BIOINDUSTRY in Japanese Dec 86 pp 55-63

[Text] To obtain high sensitivity and selectivity, immobilized enzymes are used in the detection system of high performance liquid chromatography. How they are used is discussed in the report.

1. Introduction

High performance liquid chromatography (HPLC) is excellent in separating substances, applicable in moderate conditions to polymers and polar substances being less heat-resistant and nonvolatile. It is now widely used and found to be very effective. However, a detector for HPLC highly responsive to various analytical subjects has never been developed, which has limited application areas for HPLC.

Detectors now in use are the differential refractometer, UV detector, fluorescent detector, and electrochemical detector (ECD). The differential refractometer has low sensitivity, and the others are not applicable to compounds without chromophore, fluorophore, or electrophore, respectively. In order to improve the defects, many studies have been conducted focused on producing derivatives. Among them, an online system in which immobilized enzymes are used as a detector system in HPLC draws attention because of its high sensitivity, high selectivity, and ease of use. Compounds which are less responsive to detectors are converted by enzymic reactions, and are highly responsive. Moreover, the specificity of enzymes amplifies the signals originated from particular contents in the mixture, which enables detection to be very selective. Flow-injection analysis (FIA) and enzyme electrode sensors, which also belong to analytic methods employing immobilized enzymes, are not suitable to the unified analyses of their various components.

This report focuses on the applications of immobilized enzymes to the detection system in HPLC, FIA and other sensors being discussed briefly.

2. Immobilization of Enzymes

Enzymic measurements in which enzymes are used as reagents are carefully stated in the books written by Bergmeyer.[1,2] They are widely used for measuring enzymic activities, and quantitative analyses of substrates, products, activators, and inhibitors. The enzymes often used for analyses are easily detectable oxidation-reduction enzymes; others are used in combination with these enzymes. These enzymes are liquid, and therefore they are not used in repetition. Moreover, they are unstable to heat organic solvents, and are very expensive. Immobilized enzymes have been produced in an effort to improve these defects particular to enzymes, and to use their excellent properties as much as possible. Nowadays, numerous good immobilization techniques have been developed. Widely used carriers of immobilized enzymes are chemically modified cephadex, cellulose, polyacrylamide, nylon, ceramics, glass beads, and silica gel. All of which are rigid to some extent and have a high combining ability.

The methods of enzyme immobilization are largely classified into two types: physical method and chemical method. In the former, enzymes are coated, conduct easily, but are less durable. While, in the latter method, enzymes are fixed to carriers by forming covalent bonds, and are very stable. The chemical method is often employed for the detection system in HPLC. However, sometimes enzymes are inactivated when reactions take place, and therefore it is not successful for all enzymes. This is closely studied in reference books 3)-7).

The advantages of immobilization are that enzymes themselves increase stability to heat, pH, and organic solvents, that expensive enzymes can be used repetitively and removed easily from the solution. The usefulness of so-called immobilized enzyme reactors lies in these advantages. However, there are some problems, such as the relationship between the rate of organic solvents in HPLC eluants and enzymic activity or stability, the relationship between the speed of flow and reactivity, and nonspecific absorption of products to IMER. The problems limit the application area of this method.

3. Application to the Analysis of Various Compounds

3.1 Steroid Compounds

The immobilized enzymes have been applied to the analysis of steroid compounds since late 1970's. Numerous HPLC/IMER systems have been developed.

(1) Sterols

All sterols initially taken up as analytical subjects have an absorption band near 202 nm and cannot be measured by HPLC with UV detection system. Ogren[8] has developed a detection system, in which the subjects are converted to α,β-unsaturated ketons by immobilized cholesterol oxidase with the use of the post-column method and monitored at 241 nm (Figure 1). In this case, aminated glass beads are chosen as carriers and enzymes are immobilized by the glutal-aldehyde method. Although the enzyme's stability to organic solvents are improved a little, the eluant (ethanol/water 4:1) reduces the enzyme activity irreversibly. For this reason, a buffer solution is transfused between IMER and the separation column to drop the content of the organic solvent below 20 percent (Figure 2).

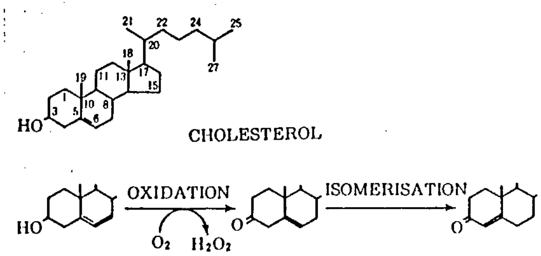

Figure 1. The Reaction of Cholesterol Oxidase

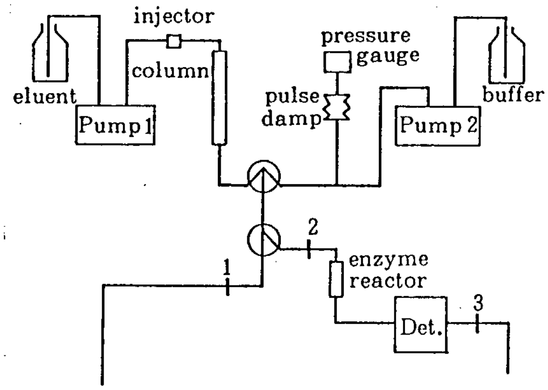

Figure 2. The Diagram of a Detection System Using Fixed Cholesterol Oxidase

Using this system, cholesterols and autooxidized sterols are measured, with a responsiveness 3.6-4.4 times as high as that detected at 211 nm without using IMER. The conversion rate by IMER is 72 percent for cholesterol, and 60 percent for 7α-hydroxycholesterol. The improvement in the conversion rate by raising the immobilization rate will lead to high sensitivity, which will make this system usable for other 3β-hydroxy-5-esteroids. However, some problems are observed, such as the complicated equipment in the post-column method, and the widening of content peaks due to absorption of IMER.

Tanabe[9] and Cho[10] studied FIA. Yao[11] developed a quantitative method to measure total serum cholesterols; this is a method in which cholesterol esterase and cholesterol oxidase are immobilized, hydrogen peroxide produced by the enzymic reaction is detected by the enzyme electrode (peroxidase) with potassium ferocianate used as a mediator. The advantage is its ease in handling.

(2) Bile Acid

The separation and measurement of bile acid is a very important diagnostic sign of hepatocholangitis. There are various kinds of bile acids in the human body; five kinds of free compounds, and their inclusions in glycine or taurine, respectively. HPLC is the most suitable method for the unified detection of these polar compounds.

Bile acid shows only one absorption band at the 17th side chain, and to form derivatives is essential in making it highly sensitive. A detection method in which derivatives are formed and then enzyme reactions occur has been studied. In this method, elements in enzymic reactions or enzymic activities can be measured with high sensitivity (Figure 3).

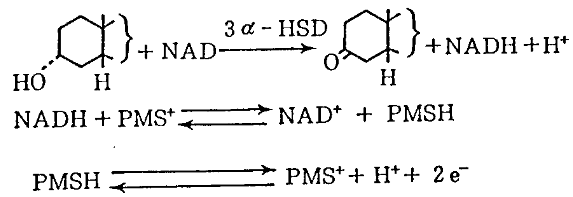

Figure 3. A Series of Reactions in Which 3α-HSD and a Mediator Are Combined

Baba[12,13] devised a method where various kinds of bile acids were separated by HPLC, then 3α-hydroxysteroid dehydrogenase (3α-HSD) and NAD^+ were transfused in the pathway, and NADH was produced in the reaction coil as a result of the enzymic reaction with bile acid which was monitored by fluorescence. This method required expensive enzymes and co-enzymes to be transfused constantly. Okuyama[14] and Arisue[15] have successively reported a system in which 3α-HSD was fixed on glass beads for detective use. This system can measure as little as 10 pmol of bile acid, and is manufactured to analyze bile acids.

Kamada[16] developed a method in which a similar IMER was employed and ECD was combined with it; in this method, NADH produced is oxidized on the glassy carbon electrode and detected as an oxidation current. This requires high voltage (> + 1.0 V) to be applied, therefore the detection by direct oxidation is not advantageous in both sensitivity and selectivity, and for this reason phenadinmethosulfate (PMS^+) is used as a mediator. As a result, reduced PMSH is electrode-oxidized by applying a voltage of 100 mV, and 20 pmol of bile acid can be measured (Figure 3).

However, these methods have some problems: IMER activity under the eluant condition to separate more than 15 kinds of bile acids simultaneously, IMER degeneration over a long period, and problems associated with the constant transfusion of NAD^+. Moreover, they are not sensitive enough to measure blood bile acids. For this reason, a method has been developed; bile acid is oxidized to 3-keto compounds by IMER, then derivatives are formed with dansylhydrazine, which are measured by HPLC with a fluorescent detective system (Figure 4).[17] This method has very high sensitivity, from 0.5 to 1.0 pmol, but it is an off-line system, and sometimes syn- and anti-isomers of produced hydrazon are separated into two different peaks.

There are reports by Bovara,[18] Carrea,[19] Schoelmerich,[20] and Heiya[21] on the application of this type of IMER to FIA.

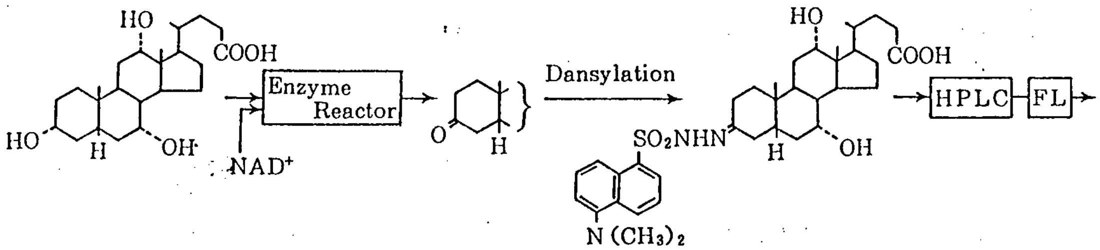

Figure 4. Induction to 3-Keto Form and Fluorescent Detection

(3) Androgen

Takagi[22)] and Wu[23)] reported methods to measure quantitatively the amount of androgen without chromophore by detecting the fluorescence of the produced coenzyme, NADH, with the use of IMER.

Serum androgen is extracted with heated ethanol, and converted to free compounds by enzymic hydrolysis with sulfatase or solvolysis. Then, they are separated by a column, and are made to react with 3β, 3α, or 17β-hydroxysteroid dehydrogenase fixed on aminated glass beads to detect the fluorescence of produced NADH.

With this method, 5-androstenedione, dehydroepiandrosterone, ethiocholanolone, and androsterone are measured quantitatively with high sensitivity; the limit of detection is 3-10 ng.

In this case, the content of the organic solvent (methanol) in the eluant must be below 60 percent. The enzyme activity in IMER reduces to only 80 percent in 1 month, even if it is washed in NAD^+ solution every day after it is used for five subjects. Although the method has such disadvantages, it is still useful for metabolic research and clinical applications of androgen.

(4) Estrogen

Estrogens are seen in our body as free-type compounds, inclusion compounds of glucuronides or sulfates. The increase or decrease is an important diagnostic sign of the fetal-placenta system.

There are various HPLC methods with the UV adsorption at ring A (λ_{max} 280 nm), but the detection-limit of these methods is unsatisfactory, approximately 0.1 nmol. On the other hand, a method using natural fluorescent light from estrogen cannot obtain high sensitivity, because the excitation wave length and that of the fluorescent waves are very similar. Moreover, each estrogen has different wave lengths, therefore some inclusion compounds cannot be detected by this method. ECD, developed as a sensitive detector for phenols and catechols, has been used in this area recently (the detection limit is 1-5 pmol). However, it is not suitable for the detection of phenolhydroxide inclusions, and some derivatives have been devised to improve the defects.[24)]

Bower[25,26] and Johnson[27] have reported a method in which estriol glucuronide is hydrolyzed by β-glucuronidase (β-G), and the released estriol is measured quantitatively by HPLC with fluorescent detection. It employs IMER in the pre-column method; when the enzymic reactions are over, the eluant is switched by a bulb, and generated estriol is removed from IMER to the separation column. Since estriol is strongly absorbed to the enzyme, it has to be desorped with a bulk solvent containing methanol; IMER is relatively stable in a 15 percent methanol solution.

This method has been applied to the quantitative measurement of gravidas urine estriol glucuronide, which has shown good results having a correlevance obtained from radioimmunoassay. It is more sensitive than UV detection, and applied not only to estriol inclusions but also estrogen inclusions. However, as materials are hydrolyzed before column separation, no information at the site of inclusion can be obtained.

Therefore, Dalgaard[28] is trying to measure estron glucuronide, by using IMER in the post-column method; in this method, bovine β-G is fixed on agarose beads, and the subject is detected by ECD. The detection limit is high, 13 pmol at S/N = 3, but it has some problems such as the relationship between the eluant and IMER, and nonspecific absorption. There is no report that it is applied to other estrogens.

3.2 Various Kinds of Inclusion Compounds

The previously discussed method to detect phenol glucuronide by the column-separation/IMER/ECD system can be applied not only to estrogen but also to other similar compounds. Dalgaard[28] has applied this method to o-, and p-nitrophenol glucuronide, phenolphthalein glucuronide as well as estron glucuronide, and has obtained good results.

Further, the same group[29,30] has developed a detection system for cyanoglycosides like amygdalin. As shown in Figure 5, glycosides are hydrolyzed by IMER, then CN^- is released by sending 2N sodium hydroxide, and finally it is detected by AG-electrode (0.0 V). Cyanoglycosides can be detected selectively with high sensitivity (detection limit 2 pmol) by this method; therefore, this has been applied to measure constituents in plans, and has obtained good results.

$$R_1-\underset{\substack{|\\ O-Gly}}{\overset{\substack{R_2\\ |}}{C}}-CN \xrightarrow{\text{Glycosidase}} R_1-\underset{\substack{|\\ OH}}{\overset{\substack{R_2\\ |}}{C}}-CN + GlyOH$$

$$R_1-\underset{\substack{|\\ OH}}{\overset{\substack{R_2\\ |}}{C}}-CN + OH^- \longrightarrow R_1R_2CO + CN^- + H_2O$$

$$Ag + 2CN^- \longrightarrow Ag(CN)_2^- + e^-$$

Figure 5. Reactions To Detect Cyanoglycosides

This system is applied to the analysis of phenol dopa (SKF 82526), having a catechol structure and being a very good drug for primary hypertension.[31] This glucuronide responds to ECD, but the oxidation potential, + 1.0 V, is higher than catechol's, + 0.6 V. Therefore, it is not always suitable for detection which requires high sensitivity and selectivity (Figure 6). For this reason, glucuronide is converted into catechol by IMER and detected. Good results have always been obtained.

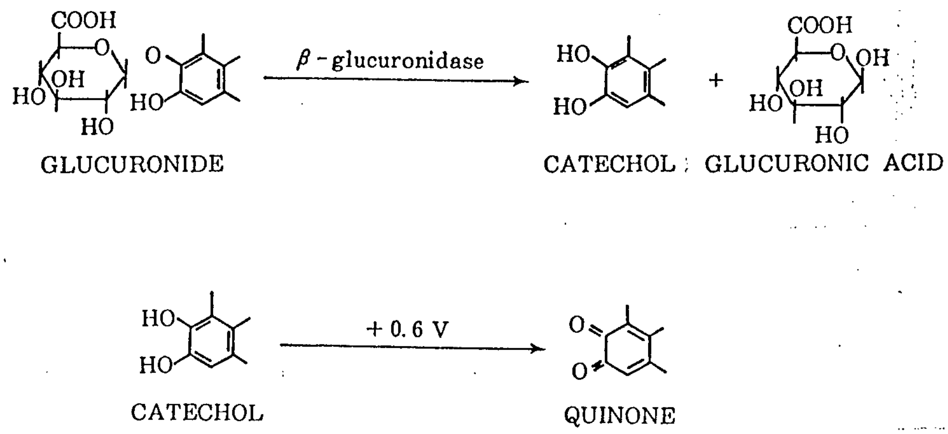

Figure 6. Reaction To Detect Phenoldopam-glucuronide

Based on the same idea, a system, where catecholamine inclusions (sulfates, glucuronides) are hydrolyzed by IMER (sulfatase/β-G), and detected by ECD, has been newly developed.[32] While a post-column method, in which perchloric acid is sent, the sulfate inclusion of catecholamine is heated and hydrolyzed, and the detection by ECD was previously reported.[33] The processes of the latter method are very complicated and the newly developed one will be better.

As for FIA, Klopf[34] treated many glucuronides with IMER, and detected released glucuronic acid by chemo-luminescent reactions. It will be applied to HPLC in the foreseeable future.

3.3 Acetylcholine and Similar Compounds

Acetylcholine (Ach), an important neurotransmitter, is present with choline in the living body, which have to be separated prior to quantitative analysis. Traditionally, Ach has been analyzed by various methods. But, these methods are not simple. The measurement by liquid chromatography has never been tried, because there was no detector with the proper sensitivity.

Recently, a process has been developed (Figure 7 (1)(2)(4)),[35] where Ach and Ch are separated by HPLC, and then treated with silica gel on which both acetylcholine esterase (Ach E) and choline oxidase (Ch O) are fixed, then generated hydrogen peroxide is measured by ECD. A required condition is to use Pt-electrode. If this condition is satisfied, the analysis with high sensitivity (5 pmol) can be conducted within 7 minutes by applying voltage of + 0.5 V.

$$\mathrm{Ach} + H_2O \xrightarrow{\mathrm{AchE}} \mathrm{Ch} + CH_3COOH \quad (1)$$

$$\mathrm{Ch} + 2\,O_2 + H_2O \xrightarrow{\mathrm{ChO}} \mathrm{betaine} + 2\,H_2O_2 \quad (2)$$

$$H_2O_2 + 2\,(Fe(CN)_6)^{4-} + 2\,H^+ \xrightarrow{\mathrm{POD}} 2\,(Fe(CN)_6)^{3-} + 2\,H_2O \quad (3)$$

$$H_2O_2 \xrightarrow{(0.5\ \mathrm{V\ vs.\ Ag/Ag^+})} O_2 + 2\,H^+ + 2\,e^- \quad (4)$$

$$(Fe(CN)_6)^{3-} + e^- \xrightarrow{(0.0\ \mathrm{V\ vs.\ Ag/Ag^+})} (Fe(CN)_6)^{4-} \quad (5)$$

Figure 7. Reactions To Detect Ach and Ch

Kaneda[36,37] applied this system to measure choline-acetyl transferase and Ach E activity; they obtained good results. Further, they developed a system consisting of column separation/GC-electrode/insoluble boric acid column/ IMER (Ach E, Ch O)/Pt-electrode, and measured catecholamine and serotonin with GD-electrode, and Ach and Ch with Pt-electrode.[38] In this case, the role of the boric acid column is to remove by chelation catecholamine which releases inhibiting peaks at Pt-electrode.

Yao[39] has developed a process in which enzyme electrodes are used for detection after Ach and Ch are separated. In this method, two kinds of electrodes, peroxidase (POD) fixed electrode and Pt-electrode, are used. In the former, potassium ferrocyanide is used as a mediator. The reduction current of potassium ferrocyanide generated by hydrogen peroxide/POD is measured (Figure 7 (3)(5)). In this case, compared with + 0.5 V in the latter, selective detection can be achieved with a low voltage of 0.0 V, and the peaks corresponding to ascorbic acid and dopamine do not appear (Figure 8).

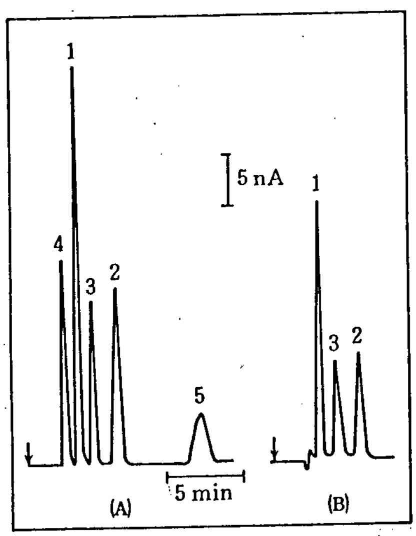

Figure 8. Chromatograms of Ach and Similar Compounds
1: Ch, 2: Ach, 3: ethylhomocoline, 4: ascorbic acid, 5: dopamine; 200 pmol for each of them
Enzyme electrode (A) ChO-Ach E, (B) ChO-Ach E-POD

Further, a chemical photogenic reaction is applied to detect hydrogen peroxide (Figure 9)[40]; dioxycetane (D) is produced by the reaction between hydrogen peroxide and bis-oxalate (2,4,6-trichlorophenol), which is reacted with perylene to generate light (Figure 10). With the most sensitive chemical photogenic reaction, the minimum of 1 pmol can be detected, which is superior to the enzyme-electrode method (Ch 1.5 pmol, Ach 2.9 pmol).

A sensor with insoluble enzymes for Ach or Ch measurement has been reported.[41]

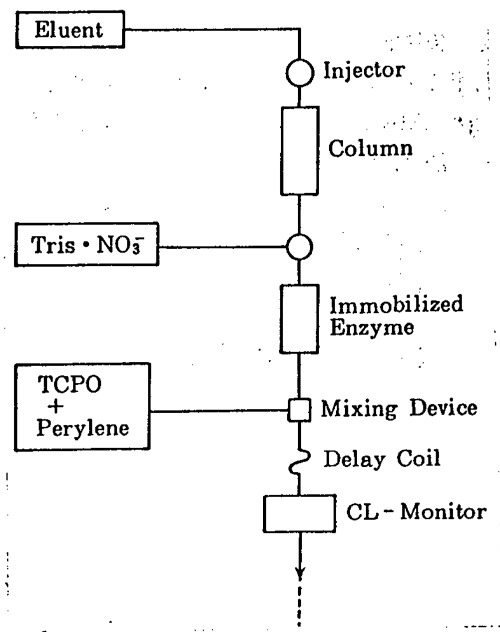

Figure 9. A Diagram of a Detection System Using Chemical Luminescence

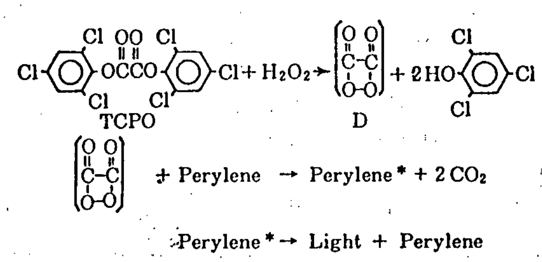

Figure 10. Chemical Luminescent Reaction by Dioxycetane

3.4 Activity Measurement of Creatine Kinase Isozymes

Creatine kinase (CK) is an enzyme catalyzing the energy metabolism of muscles, consisting of three isozymes. The activity of this enzyme in the blood is a diagnostic sign of heart and muscle diseases. To measure CK activity, Rosalki's method[42] which employs coupling enzymes, hexokinase (HK) and glucose-6-phosphate dehydrogenase (G6PD) (Figure 11) has often been used. HPLC has also been studied since Kudirka[43] reported on it.

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{Creatine} + \text{ATP}$$

$$\text{ATP} + \text{Glucose} \xrightarrow{\text{HK}} \text{ADP} + \text{Glucose-6-phosphate}$$

$$\text{Glucose-6-phosphate} + \text{NADP} \xrightarrow{\text{G6PD}} \text{Glucono-}\delta\text{-lactone} + \text{NADPH}_2$$

Figure 11. The Principle Reactions To Measure CK Activity

Denton[44] devised a system where isozymes are separated by HPLC to react with CK, then treated with IMER (HK/G6PD), and generated NADPH is detected by fluorescence. Schlabach[45] has also developed a similar system. In these methods, agarose or aminopropyl glass are used as the fixing carrier, but both of them do not satisfy the condition for rigidity and fixation. Recently, Hayashi[46,47] has successfully developed an analytical method having high sensitivity (detection limit 15 pmol) and stability for a long period by using IMER with a gel fluorine compound fixed as a carrier.

While, isozymes of lactate dehydrogenase can be measured by a similar system, the measurement of lactic acid itself is generally performed by sensors or FIA with fixed lactate dehydrogenase.[49-51]

3.5 Other Compounds

Kiba[52] reported on a system in which various amino acids are separated with an inverted phase column, reacting with fixed L-amino acid oxidase to produce hydrogen peroxide and homo-vanillinic acid are treated with fixed POD to generate fluorescence to be detected. The minimum detection limit of this process is 0.25-0.5 nmol, which is no better than the traditional method of forming derivatives in sensitivity and separation rate.

Urea in serum or urine is important as a diagnostic sign for renal function, and some sensors have been developed. Jansen[53,54] developed a system where urea and ammonium are separated by ion-exchange chromatography, and urea is converted to ammonium by fixed urease, this ammonium reacts with o-phthalaldehyde to detect fluorescence. The minimum detection is 0.4 ng for urea, and 0.3 ng for ammonium.

Meek[55] reported on a method in which inositol phosphates are separated by an anion-exchange column, react with fixed alkaline phosphatase and the generated inorganic phosphorus is detected as molybdenum blue with a detection limit of 1 nmol.

4. Conclusion

In this report, the application of immobilized enzymes as HPLC detection systems, classified in accordance with compounds, has been discussed. It is certain that this method has some advantages: It can detect with high sensitivity and selectivity compounds being less responsive to detectors, and it can use expensive enzymes in repetition. However, as discussed in the preceding sections, due to the relationship between organic solvents used as eluants and enzymic activities, separation and detection influenced each other. Moreover, IMER degenerates in approximately 2 to 3 months in repetitive use, and therefore, how to stabilize them should also be discussed further.

At present, these systems are applied mainly to clinical analyses. Further development in other areas is expected in the future.

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COMPUTER AIDED PROTEIN DESIGN (CAPD) DISCUSSED

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[Article by Haruki Nakamura, assistant, Physics Engineering, Engineering Department, Tokyo University]

[Text] Computer aided protein design (CAPD) which would enable systematic design of new artificial proteins through the use of structural energy calculation of protein and molecular graphics has been awaited. The present status and issues of that technology will be explained in a practical manner.

1. Introduction

When developing new artificial proteins based on protein engineering, every developer has a challenging objective, scientific or engineering. CAPD is a technology that is expected to provide a systematic preliminary design of amino acid sequence meeting that objective. This technology is considered analogous to CAD (computer aided design) in LSI, machine and architecture designs.

Figure 1 shows comparison flowcharts of CAPD and CAD technologies. Portions enclosed by — - — in the figure represent creature-independent CAPD and hardware-independent CAD, respectively. Once a system represented by this flowchart is established, automated design of an artificial protein can certainly be expected; there are many issues at present. The scientific infrastructures (portions enclosed by ----) on which technologies in each stage of CAPD depend, involve probability and empirical rather than determinative factors (unlike CAD). This increases the gap between the real and anticipated possibilities of CAPD, with anticipated CAPD possibilities exceeding current reality.

The author will introduce structure forecasting/analyzing methods and molecular graphics technology that stand behind CAPD technology, describe examples of CAPD that the author experienced while staying at Leeds University, England, in 1985, and finally propose future trends including wishful thinking.

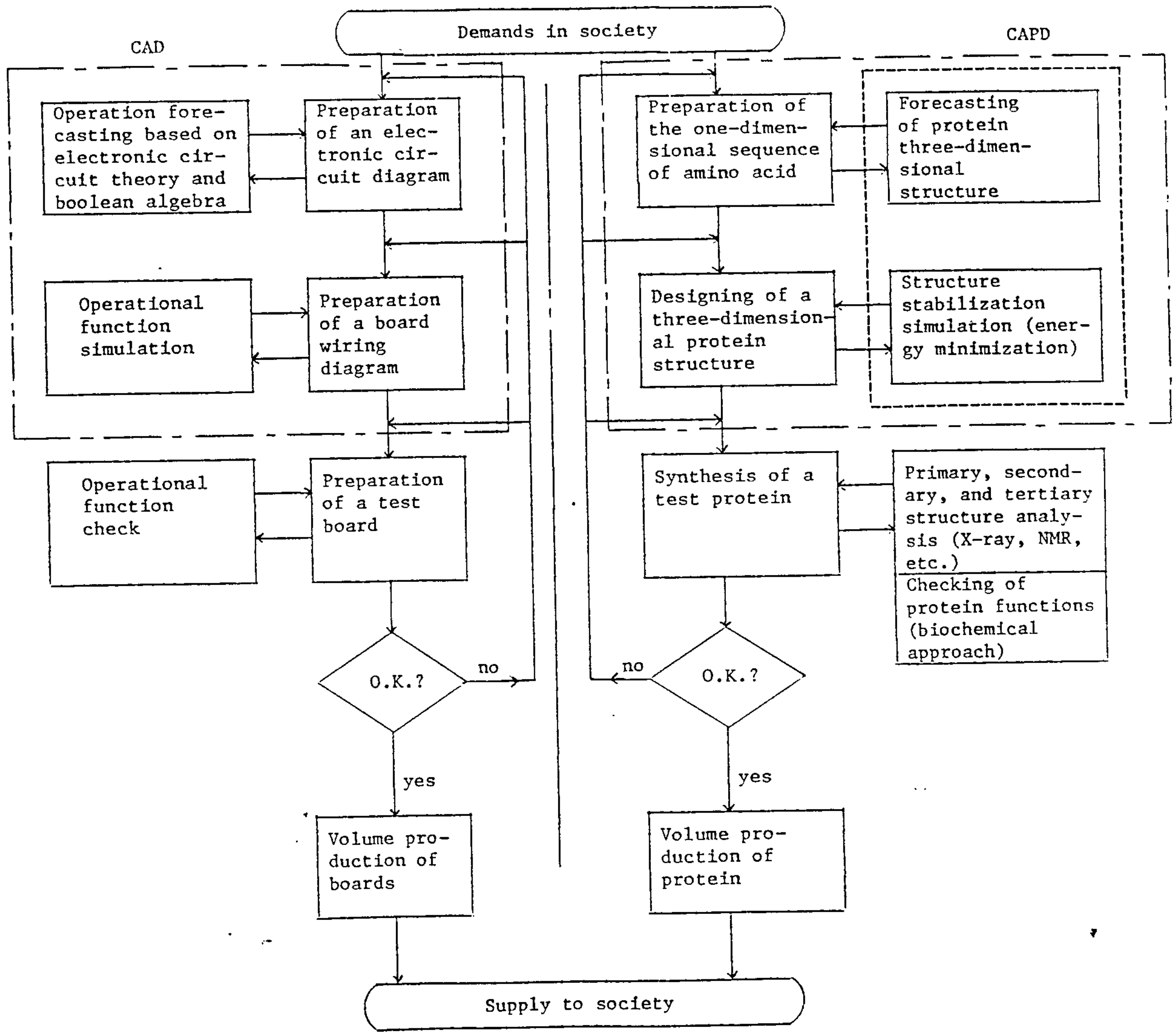


Figure 1. Protein Engineering Flowchart and Positioning of CAPD Flowchart of Electronic Circuit Board Design by CAD on the Left Half, and That of Corresponding Design by CAPD on the Right Half

2. Computer Assisted Protein Structure Forecasting/Analyzing

(1) Structure Forecasting

Since the structure stabilization and function implementation of protein heavily depend on its three-dimensional structure, CAPD technology presupposes a three-dimensional structure of a new protein in one form or another. Although it is ideal that, as shown in Figure 1, a three-dimensional structure (tertiary structure) can be forecast from the amino acid sequence (primary structure) of that new protein, no practical technique has been developed up to now that permits the direct forecasting of a tertiary structure from a primary structure alone. At present, forecasting a partial structure (secondary structure) such as α-helical and β-sheet structures from a primary structure is successful only 70 to 80 percent. Methods for forecasting a secondary structure from a primary structure can be obtained from bibliographies 1) through 4). The author here will describe methods for forecasting the structure of a protein which is very similar to one whose tertiary structure is known.

Two methods are available. With one method, one builds a model using a molecular model or molecular graphics; with the other, the minimum value of protein structure energy is searched.[5-8]

The former method has an old history; the three-dimensional model of α-lactalbumin which is 50 percent homologous to lysozyme in the primary structure was built[10] immediately after the X-ray crystal structure analysis of egg white lysozyme had been performed by D.C. Phillips.[9] A recent example in which the three-dimensional structure of renin was forecast by T. Blundell, et al., through the use of molecular graphics is famous.[11]

An example of the latter method is a paper by H.A. Scheraga, et al., which describes structure energy minimization that is based on the above forecast structure of α-lactalbumin.[12] This method will be effective for forecasting the structure of a new protein which is generated by performing site-directed mutagenesis on a protein whose three-dimensional structure is known. Details will be described in Section 4.

(2) Structure Analysis

A new approach which more actively uses a computer has emerged in the structure analysis of new proteins.

X-ray crystal structure analysis is and will be the most important technique in identifying three-dimensional protein structure at atom level resolution. In particular, a molecular replacement method[13,14] which has been proposed as a useful method for phase determination of a scattering factor has the advantage of permitting the omission of heavy-atom mono-type substitution crystal creation, one of the causes behind the difficulty of X-ray analysis; it is expected to be very effective for the structure analysis of a new protein on which site-directed mutagenesis has been performed.

Since X-ray crystal structure analysis involves the problem of lacking an established protein crystallization approach, a structure analysis method using the nuclear magnetic resonance (NMR) method which requires no crystallization has recently been attracting attention.[15] Especially, the distance geometry method[16,17] that analyzes the Nuclear Overhauser Effect (NOE) signal whereby nuclear-spin-to-nuclear-spin distance information can be obtained has become competitive with X-ray analysis in analyzing proteins with light molecular weights.[18,19] Although it has disadvantages in that reverting an NMR signal to each spin with a protein is difficult when the molecular weight is 10,000 or larger, and also any one error in reverting to a spin will significantly affect the entire structure, it is a very promising and rapidly developing field.

From a biochemical/pharmaceutical point of view, a structure surrounding an active portion rather than the entire protein structure is of interest. A transferred NOE approach is used to obtain the tertiary structure of a substrate linked to a macroprotein.[20-22] The author has developed an approach whereby the existence probability region of a site-unknown nuclear spin can be expressed in contour lines based on the multiple surveying principle (Figure 2).[23] This approach, when used for measuring NOE between protein and substrate, can estimate the structure at the substrate link portion of a protein.

3. Role of Molecular Graphics in Protein Engineering

(1) Understanding Natural Protein

The designing of protein starts with the partial modification of natural proteins. Therefore, the designer of a new protein must be familiar with natural proteins. In general, protein consists of macropolymers with a molecular weight of several ten thousand, and each molecule has its own three-dimensional structure; the designer must identify its steric image.

More than 280 different atom coordinates subjected to structure analysis to X-ray analysis research around the world are now stored in the protein data bank (PDB),[24] and using those coordinate molecular values are displayed on a graphic screen in the form of various models and representations. Using colors for displaying the physical properties and biological information of protein on a color-graphic terminal will be more effective.[25-28]

It is true that watching and handling molecule models everyday that have actually been built is the best way to become familiar with three-dimensional structures. However, it is also true that molecular graphics are important. A recently developed and marketed stereo viewer (Photograph 1 [omitted]) is very effective and molecular graphics are more effective than molecule models in understanding the dynamic aspects of proteins.

(2) Tenative Generation of New Protein and Its Validity Review

Next, the protein designer should forecast a structure where new peptide chains are generated based on the natural protein structure, and check whether the structure is compatible with the designer's objectives. Practical work at present involves performing site-directed mutagenesis on a graphic screen, forecasting a new protein structure through calculation, and redisplaying the results.

(3) Supporting the Structure Analysis of Newly Generated Protein

When the newly designed protein is actually generated, structure analysis described in the preceding section is needed. With X-ray analysis, FRODO[30] is used to assign protein atoms to measured electron densities in a real space. With the distance geometry method, where NMR is used, an initial structure is generated[31] based on proton-to-proton distance obtained from NOE signal analysis and a structure after optimization is displayed.

As mentioned above, molecular graphics play an important role in protein engineering. Although, personal computers are powerful enough for displaying protein molecules alone,[32] dedicated computer graphic terminals linked to a medium/large host computer may be required for the design and structure analysis of a new protein. Particularly, since molecular graphics handle the three-dimensional steric image, a three-dimensional graphics system or workstation is more effective and places a lighter burden on the host computer in connection with image display and provides real-time and interactive rotation, transfer, enlargement/reduction, and structure generation of molecules and replacement atoms.

4. Examples of CAPD

4.1 Scope and Objective of Design

Dihydrofolic acid reduction enzyme (DHFR) has a catalytic action that reduces dihydrofolic acid to tetrahydrofolic acid, and is an important purine biosynthetic enzyme. Therefore, this enzyme inhibitor slows down DNA synthesis in a cell and is sometimes used as a cancer suppressor.[33] The structure and functions of DHFR have been extensively studied, various enzymes derived from bacteria to Mammalia have been refined, and their amino acid sequence is known. In addition, more than five to six enzymes including those not announced have been X-ray analyzed.[34-38]

Natural DHFR requires NADPH as a hydrogen donor during the reduction process of dihydrofolic acid; while NADH with a similar structure can link to DHFR with an affinity one-hundredth that of NADPH.[39] Therefore, L. casei derived DHFR was selected to perform site-directed mutagenesis on the amino acid surrounding the NADPH link portion. In this way, a new enzyme design was attempted that intends a change in which the new enzyme required NADH rather than NADPH.

4.2 Design Technique

The author had to grope his way in the dark when he started to use a design technique which was unknown. The author used molecular graphics to visualize desirable amino acid substitutions based on his subjective thinking in an

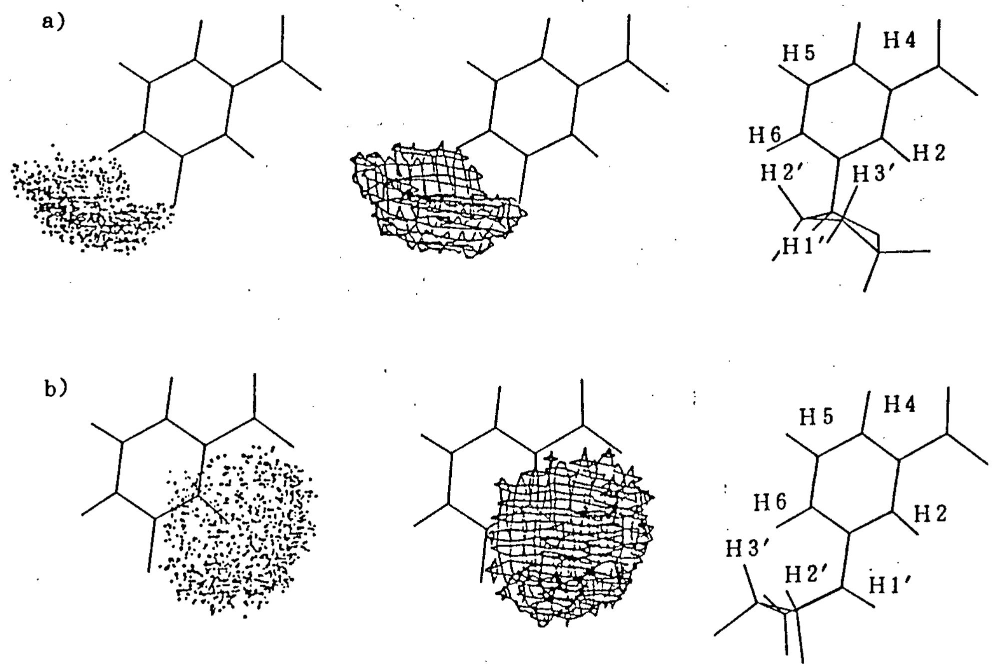


Figure 2. Analysis of Active Portion of Protein by Multiple Surveying

The existence region of H_N1' nucleus spin of NAD^+ linked to heat-resisting germ derived lactic acid dehydrogenation enzyme is shown by dots (left) and contour lines (middle).[22,23] On the right is shown the structure of NAD^+ nicotine amide portion optimized under these conditions. In a) allosteric effectors fructose 1, 6-bisphosphate are not linked, and in b) they are linked.

attempt to find realizable structures. However, this approach soon came to a standstill because of the lack of objective indicators, and the author found that a more systematic approach should be predetermined.

Figure 3 shows the flowchart of an arranged design method. First, amino acid substitution portions and new amino acid candiates that are expected to meet the objectives described in 4.1 are searched; as many candidates as possible should be searched. Next, those candidates are narrowed down, by means of molecular graphics and local structure energy calculation of substitution portions, to ones which are subjected to structure energy minimization in terms of a whole molecule of substrate-involving complex system. In this way the structure of a new enzyme candidate is forecast. Finally, the candidate undergoes a quantitative evaluation for conformity with the initial objective.

If an amino acid substitution with better evaluation results is searched after some feedback, a reasonably objective design can be implemented.

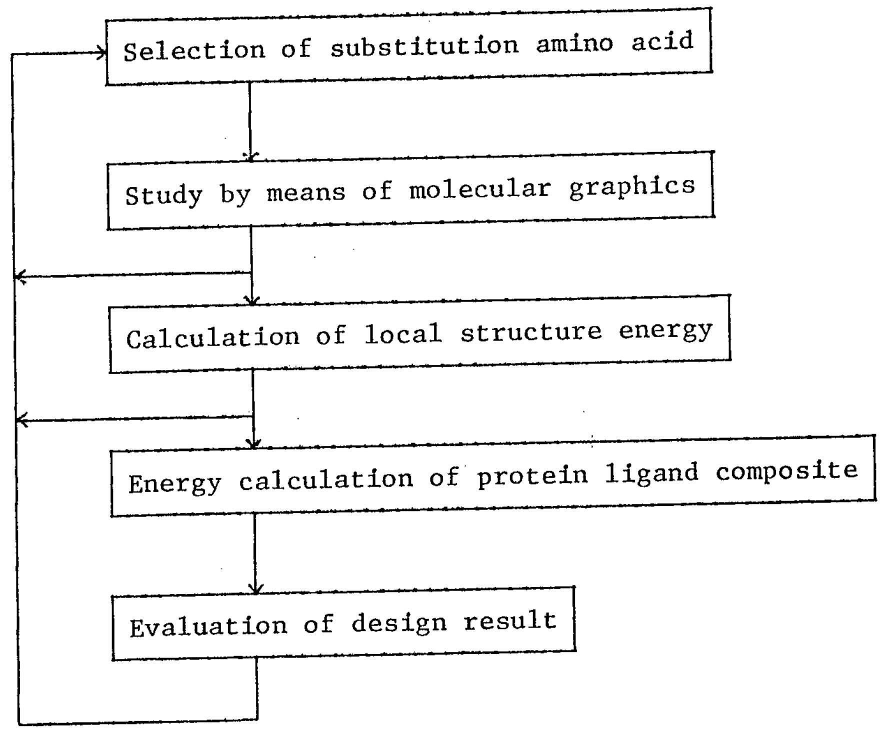


Figure 3. CAPD Flowchart

4.3 Selection of Substitution Amino Acids

Even if the design proceeds successfully in accordance with the steps in Figure 3, an actual peptide chain cannot necessarily be folded as desired because of various hypotheses set up during structure energy calculation. We, novice designers, rather like to have a substitution amino acid set up that could be folded in the same manner as a natural protein. In other words, fewer amino acids that are to be substituted concurrently are desired, and the properties of new amino acids to be substituted should be similar to that of a natural protein. During the selection, it is important to consider the equivalent enzymes of other species and amino acid sequences of similar proteins.

Although several possible amino acid substitutions were studied as new enzyme candidates that provide stronger bonding of NADH in place of NADPH, as called for by the initial objective, they were narrowed down to the following two candidates in the final stage (see Figure 4).

1) Thr 63 is substituted for amino acid (Asp of Glu) with negatively charged side chains so that it can be electrostatically repelled against NADPH and hydrogen bonded with NAKH.

2) Thr 63 is substituted for amino acid (Gln) with long-polarity side chains so that it can be repelled against NAKPH in terms of steric hindrance and also hydrogen bonded to NADH.

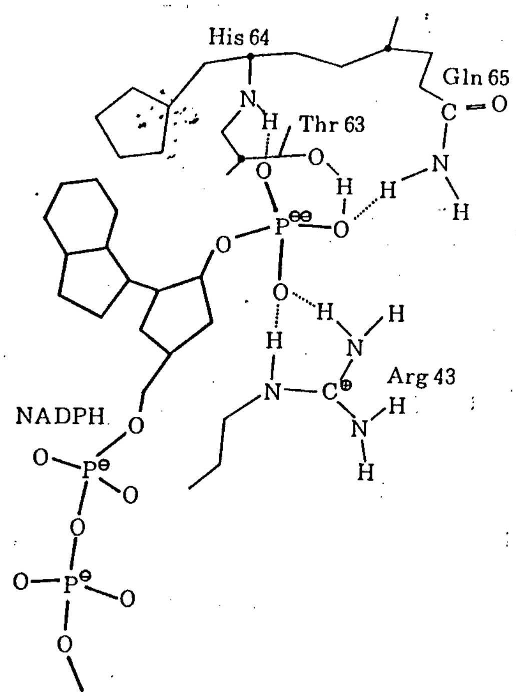


Figure 4. Diagram of NADPH Bonding Portion of L. casei Derived DHFR

2'-phosphoric acid portion forms a hydrogen bond/ion bond network together with Thr 63, Gln 65, and Arg 43.

4.4 Computer Supported Design

On the basis of the steric structure of natural proteins obtained by X-ray crystal structure analysis, the structure of a new enzyme that has been amino acid substituted is displayed using molecular graphics. During this process, that structure is compared with that of the natural enzyme on the condition that the side chains of the new enzyme alone can move freely. Although it is possible to move the side chains of the other amino acids, that attempt will widen the gap between the new and natural enzyme structures, reducing a chance of ensuring correct folding.

It is effective that local structure energy calculation is used as a design guide with molecular graphics used only for identifying a displayed structure. The calculation is performed while a degree of freedom is given only to dihedral angles involving atom-to-atom covalent amino acid side chain bonds to be substituted, and the other surrounding side chains and principal chains are fixed. If the calculated energy is high and no stability point is found (although the possibility of that amino acid substitution cannot be denied if the softness of an enzyme structure can be assumed), it is better to remove that structure from the list of initial candidates.

This locally optimized structure is picked up as an initial structure, a degree of freedom is given to all atom coordinates involving enzyme or substrate composites, and the structure energy of the entire system is calculated and minimized.

With the example of DHFR, it looked possible to the author to permit Thr 63 → Glu 63 and Thr 63 → Gln 63 on the graphic screen, but results of a local structure energy calculation forecasted that the side chains of Glu or Gln could not extend to the active portion side of DHFR because of steric hindrance and that they will not directly interact with NADPH or NADH. Finally, it was found that a Thr 63-to-Asp 63 substitution was most promising. However, it was supposed that when this new enzyme formed a composite with NADPH, an Asp 63 side chain is located inside DHFR, generating slight repelling power against NADPH. Therefore, Val 75-to-Met 75 substitution was performed concurrently so that Asp 63 can directly interact with 2'-phosphoric acid of NADPH; this was our final design.

A composite structure consisting of this variant (Thr 63 → Asp 63, Val 75 → Met 75) and, NADPH or NADH, was forecast using energy refinement of the entire system. The result is shown in a) and b) of Figure 5. It shows that while the dissociated Asp 63 forms a hydrogen bond with OH of 2'-portion of NADH, Asp 63 electrostatically repels the 2'-phosphoric acid portion of NADPH.

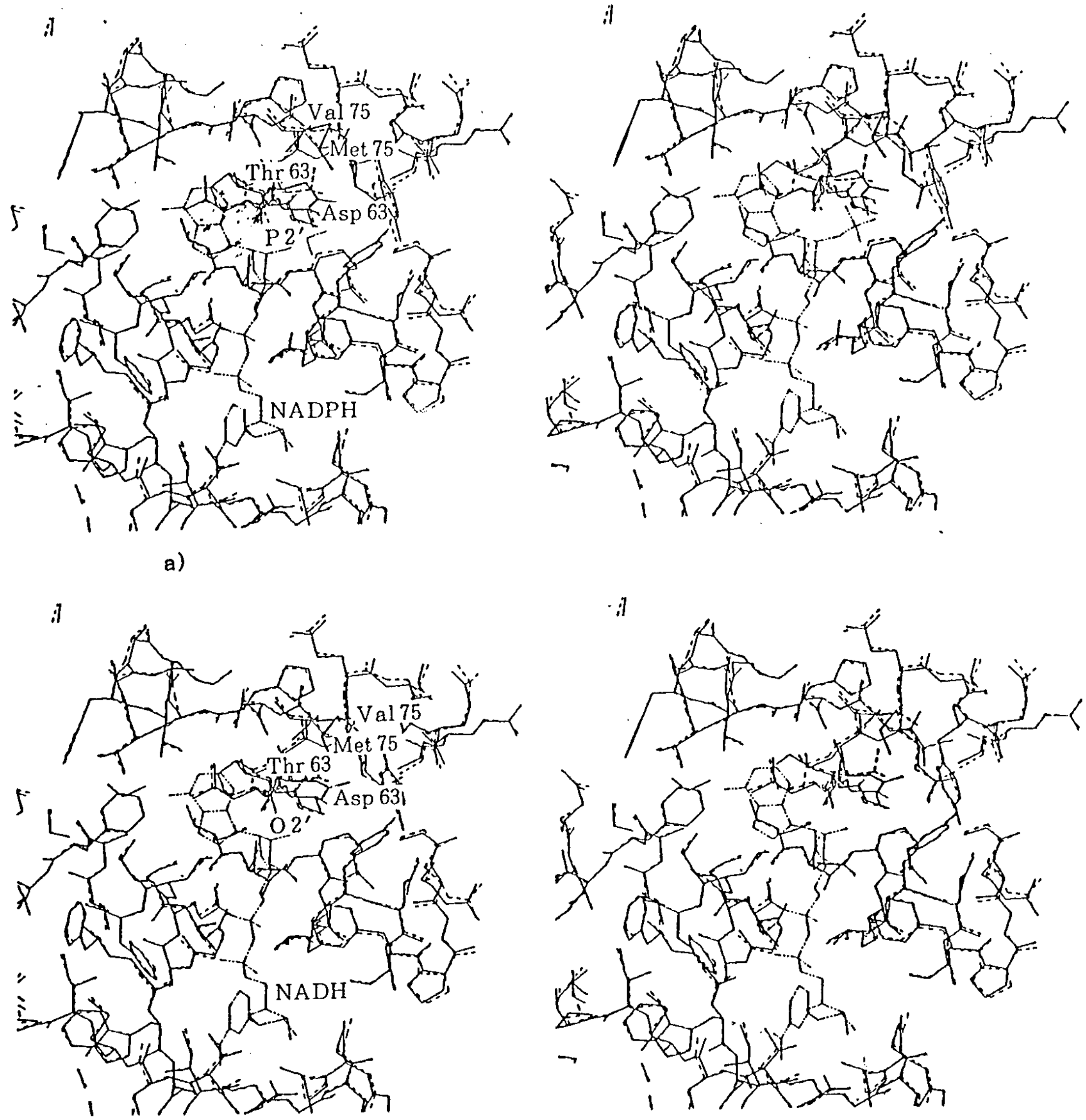
4.5 Evaluation Calculation

If a desk calculation can evaluate the functions of a candidate protein before those of a new enzyme actually produced are evaluated, work efficiency will be significantly improved. With the design example of DHFR, energy bonding of a variant (Thr 63 → Asp 63, Val 75 → Met 75) with NADPH or NADH is calculated and compared with those obtained with natural DHFR.

Nevertheless, those calculated values lack quantitative features that permit direct comparison with experimental ones. For example, a quantitative discussion on hydrogen bond energy and electrostatic interaction presents problems, because an accurate estimation of an electrostatic blocking effect caused by a solvent molecule such as water or a low molecular ion is difficult. In addition, a free energy change generated when a solvent is changed from water to oil can be obtained from the calculation of a surface area exposed to the solvent,[40] and the hydrophobic interaction change resulting from substrate or coenzyme bonding can be estimated.[41] However, parameter accuracy is unsatisfactory and therefore a quantitative discussion is far from satisfactory.

5. Future Image of CAPD

As mentioned above, CAPD technology involves various problems to be solved and automated design is still in the distance. Even if the discussion is limited to site-directed mutagenesis, it is essential to streamline tasks in Figure 3 for increased accuracy. More practically, use of a database and support by an expert system based on an artificial intelligent technology in the selection of a substitution amino acid in Figure 3 will be helpful for



a)

b)

Figure 5. Stereo-diagram of Coenzyme Bond Portion of DHFR Variant (Thr 63 → Asp 63, Val 75 → Met 75)

Variants obtained by energy refining a coenzyme-involved entire composite system.
a) NADPH involved composite. The solid line shows the variant, dotted line natural DHFR, two-dot chained line NADPH, and thick line substitution amino acid residue portion.
b) NADH involved composite. The solid line shows the variant, dotted line natural DHFR, two-dot chained line NADH, thick line substitution amino acid residue portion.

the selection of more objective candidates. Although the analysis of the secondary structure/ultra secondary structure of protein has started using PROLOG language,[42,43] the contents of the database is very poor. The database should be enriched and expanded in step with the development of protein engineering as a whole. There are problems awaiting a quick solution, such as more accurate parameters used in structure energy calculation and evaluation calculation, solvent molecule estimation, and more accurate evaluation of electrostatic blocking effects made by solvents.

Longer-range issues include the design of utterly new amino acid sequences in addition to site-directed mutagenesis,and the estimation of substances otherthan 20 natural amino acids. Intuition-dependent design using molecular graphics and molecular models only is almost powerless for resolving those issues. Instead, future designers will be supporte d by expert systems based on databases rich in structure and function and by structure energy calculation which is more quantitative and faithfully describes actual protein systems.

6. Conclusion

The author attended the fifth annual meeting of the Molecular Graphics Society, an international organization, held at Cap d'Agde, South France, in April 1986. I noticed that the methodology (display method) of molecular graphics had already been exhaustively discussed, and that the attendees' attention was moving toward structure analysis experiments, theoretical calculation, artificial intelligence, and bonding.

In Japan, partly because graphic system hardware costs are high, CAPD study particularly at universities lags behind that in other countries. It is still an immature technology full of many problems, and we, late starters, have many problems to be resolved.

Finally, it should be noted that the new enzyme design work involving DHFR was performed with the support of the 1985 British SERC.

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APPLICATION OF LASERS IN THE CHEMICAL INDUSTRY DISCUSSED

Tokyo OPTRONICS in Japanese Oct 86 pp 78-82

[Article by Akira Yabe, a member of the National Chemical Laboratory for Industry, the Industrial Science and Technology Agency, MITI]

[Text] Introduction

Whereas, in the sector of basic science, application of laser has brought out history-making results in laser chemistry such as spectroscopy of ultra-high resolving power, analysis of high-speed phenomena, and ultra-high fluorescent analysis, its applications in the chemical industry, an applied science, is still underdeveloped compared with those for other industrial sectors such as the electronic, the mechanical, and the medical-equipment ones. Research on the laser beam process, nevertheless, have recently begun to be activated in the chemical industry along with progress in projects or the practical application of uranium-isotope enrichment and in apparatuses for excimer laser. This paper will summarize the present status of research in the chemical industry and the kinds of lasers that are eagerly sought by industry.

2. Laser and Chemical Reaction

Excitation in chemical reaction involves excitation of molecules either to a vibrational-excitation level or to an electronic-excitation level: The former is produced by an infrared laser involving an oscillating photon energy of the order of magnitude of 0.1 eV (3 kilocalories for each mole or 6×10^{23} molecules) and the latter, by visible, ultraviolet, and far-ultraviolet laser with oscillating photon energy of several eV or more. The splitting of the ordinary chemical bond requires an energy of over 3 eV (80 kilocalories for each mole) and this implies that a multiple photon absorption amounting to a few score of photons is necessary in the case infrared laser is applied. In ultraviolet lasers, in turn, it has been reported that electrons are excited to higher energy levels or ionized by means of multiple-photon absorption produced by a collected beam of high luminescence, leading to special chemical reactions. (Figure 1)

In the early stages of laser research, researchers aspired to materialize dreams for a possible chemical reaction of selective combination of substances by means of vibration excitation of a particular bond produced by virtue of

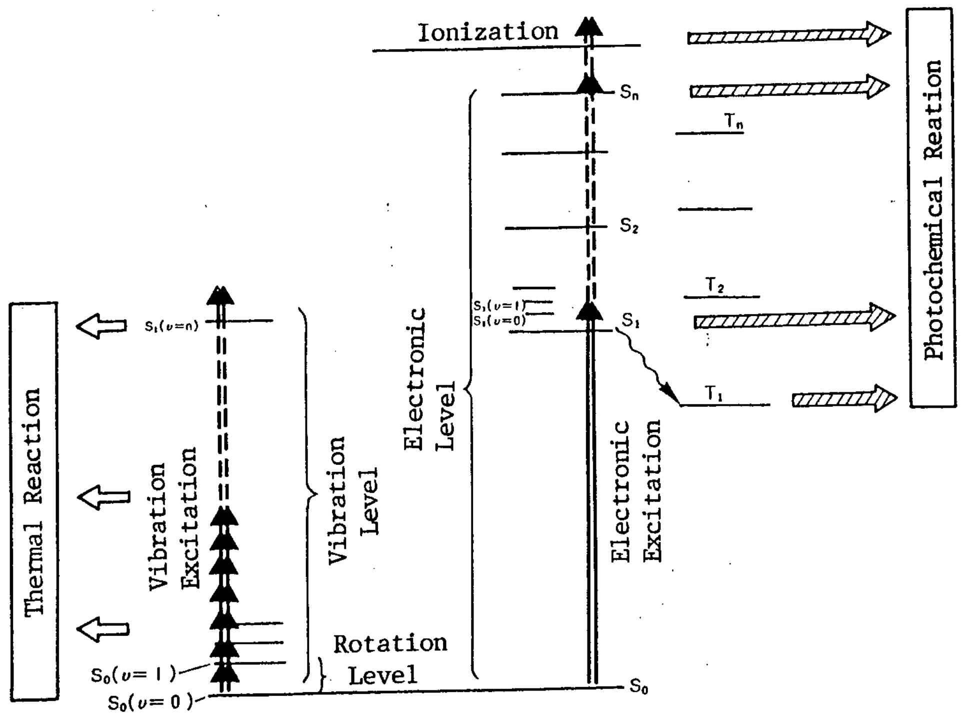


Figure 1. Lasers and Relevant Chemical Reactions (Vibration Excitation and Electronic Excitation)

the superior monochromic property of the beam. It has proved, nevertheless, that the energy introduced through the "window" of a particular bond is subjected, in most cases, to a rapid intra-molecular relaxation process and hence end up in splitting the bond involving the lowest energy for cleavage, the result of common thermal reaction, though hope has still been pinned on the infrared laser of high-output, ultrashort pulse (pico-second region) for a possible reaction of selective combination.

One of the important applications of infrared laser in the chemical industry is in the enrichment of isotopes. Another application isin pyrolytic decomposition reactions where the laser serves as a high-intensity, short-pulse, thermal beam allowing rapid heating and cooling.

After infrared lasers disappointed chemical researchers in connection with reactions of selective bonding, the chemical industry has pinned its hope on high output ultra-violet laser. Many research results have been built up for photochemical reaction using stationary light of, e.g., the mercury lamp. Industrial processes involving the relevant reaction have materialized in the manufacture of nylon materials, medicines, perfumes, etc. Photochemical reaction process has been spotlighted because it allows synthesis of compounds which are not amenable to thermal synthesis, because it allows direct synthesis of compounds which, in thermal reaction, require multiple stages of process for their synthesis, and because it allows high yields and highly selective synthesis by virtue of the reaction proceeding even at low temperatures. Ultraviolet laser, if its applications are to be put on the market, needs to promote photochemical reactions using the stationary light which has so far been developed. Its application, therefore, comprises largely either (1) one which involves a special laser reaction, a reaction which takes place by the application of stationary light but is facilitated by the application of the laser on the basis of the properties of the beam, or one (2) which involves a reaction wherein application of the laser is superior to that of the stationary light in terms of industrial process, e.g., productivity (selectivity, yield) and economy.

In Table 1 are listed the characteristics of ultraviolet lasers which are utilized as technologies for the control of chemical reactions. Though such applications as given in the table are possible, the rate of generalization of laser apparatuses is still very low in this sector of industry. Relevant research has to date been limited to chemical corporations in the United States and research institutes in the Soviet Union and Germany.

3. Present Status of Research on Laser Chemical Process

3.1 Laser-Induced Chain Reactions

Max Planck Institute in 1979 announced a synthetic process for the manufacture of vinyl chloride monimer, the raw material of vinyl chloride resin, with the use of excimer laser. A plan for the construction of a relevant pilot plant with a production capacity of an annual 1,000 tons was rumored for a while. The institute thus was made the focus of attention of the chemical industry. The reaction involves irradiation of dichloroethane, the raw material, with KrF- or ArF- laser such that a relevant C-Cl bond is cleaved; the reaction,

Table 1. Control of Chemical Reactions by Means of Excimer Laser

Features of the Laser	Possibility for the Control of Chemical Reactions
Monochromicity	The laser is capable of exciting particular molecules to particular energy levels in a selective manner. Its energy distribution is far narrower than for the mercury lamp, etc. Side reaction may be removed.
High Strength	Since its power density is enormously larger than for the conventional arc lamp, it can produce high concentrations of excited activated species. It can also produce a high grade of excited state by means of multiple-photon absorption process.
High Coherency	The laser can produce exicted species locally and allows the action to proceed without being affected by the hot wall effect of the reactor. Its multiple-photon reflection serves to raise the efficiency in the absorption of light by the reactants.
Pulse Formation	The laser allows the reaction to be completed in ultrashort time, thereby preventing secondary absorption of light by excited activated species and products and, hence, raising the efficiency of the reaction and blocking side reactions.

starting with the cleavage, includes a subsequent growth process by virtue of which efficiency as high as a quantum yield of 5,000 is attained (at a reaction temperature of 300 degrees C, yield of 5,000 molecules for each photon).

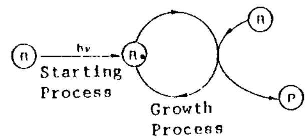
Chain Reaction System

[Starting Process] $CH_2ClCH_2Cl \rightarrow CH_2Cl\dot{C}H_2 + Cl\cdot$

[Growth Process] $\begin{cases} Cl\cdot + CH_2ClCH_2Cl \rightarrow CH_2Cl\dot{C}HCl + HCl \\ CH_2Cl\dot{C}HCl \rightarrow CH_2{=}CHCl + Cl\cdot \end{cases}$

[Termination Process] $Cl\cdot + CH_2Cl\dot{C}H_2 \rightarrow CH_2{=}CHCl + HCl$

R - reacting molecule
R. - radical
P - product



The above reaction, when carried out thermally, requires a reaction temperature of above 500 degrees C; application of the laser, in contrast, allows the reaction to proceed at low temperature, which serves to conserve energy and to be a process of high yield and high selectivity.

The major difficulty that acts adversely to the introduction of the optical process in comparison with the thermal for the chemical industry is the high cost of photons. In the above chain reaction, though involving manufacture of a raw-material chemical, the photon cost is diminished by the factor of the reciprocal of the quantum yield, thereby rendering the laser process available for the manufacture of the chemical.

Among other examples of similar reactions are the synthesis of cumene hydroperoxide, the raw material of phenol, which involves irradiation of cumene with XeCl-laser under an oxygen atmosphere, leading to the cleavage of a C-H bond and a chain reaction with a quantum yield of 500, and that of methylene chloride [as published] by the chlorination of methane, with a quantum yield of 50 to 270,000 by irradiation with KrF- or XeCl laser.

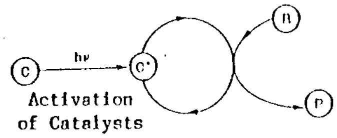
3.2 Laser-Induced Catalytic Reaction

As in the chain reaction above, a repeating or turnover reaction goes ahead by virtue of the activity of a catalyst and affords the intended product with a high quantum yield, which serves to enhance industrial operation.

[See Figure 2]

In comparison with the conventional chemical catalytic reactions, the laser induced one involves high catalytic activity under mild conditions, furthermore, by virtue of the following features of the reaction: 1) the reaction proceeds at low temperatures and hence is free from adverse effects due to high temperatures; 2) it allows selective excitation of exclusively catalyst precursors and hence serves to save energy; 3) irradiation of pulse laser allows generation and regeneration of active catalyst species at very short time interval.

The shift reaction of water gas given by $CO + H_2O \rightarrow H_2 + CO_2$ makes an industrially important process for raising the concentration of hydrogen in the synthesis gas and is currently carried out at a high temperature and pressure of around 400 degrees C and 30 atm. with the use of an oxidation catalyst. It has been found, however, that the reaction proceeds at 5 to 65 degrees C under



[Cycling of catalysts]
(Turnover)

Catalytic Reaction System

(R=reacting molecule; C=catalysts; C*=activated catalysts; P=products)

Figure 2.

Table 2. Estimates of Excimer Laser Units for the Manufacture of Bulk Chemicals (Standard Oil Co., K. V. Reddy)

Chemicals	Annual Production		Quantum Yield	Total Output of Laser Beam Required (kW)	Number of Units of the 100-watt Lasers Required
	kg/year	mol/year			
Vinyl chloride	3.02×10^9	4.90×10^{10}	10,000	110	1,100
Raw material of phenol (cumene hydroperoxide)	1.14×10^9	1.21×10^{10}	1,000	190	1,900

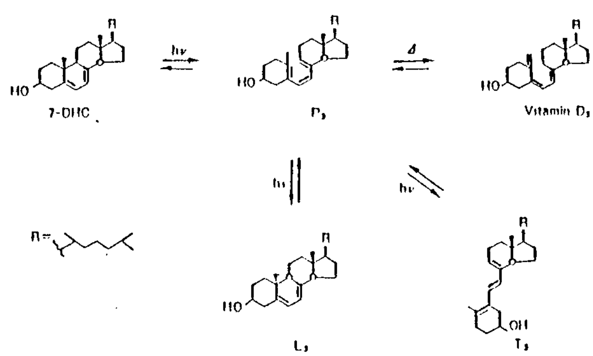


Figure 3. Synthetic Process of Vitamin D by Photochemical Reaction

extremely mild conditions and the relevant concentration of hydrogen is raised up to as much as 1.4 to 2.1 times by means of N_2-laser irradiation of $Cr(Co)_6$ or $W(Co)_6$ in a basic solution of a mixture of H_2O and methanol.

Since research on photocatalytic reaction, which is also important industrially, has been promoted recently, introduction of lasers into research institutes in the coming years is expected to lead to an active expansion of the research.

3.3 Photochemical Processes of High Yields Based on Monochronic Laser Beams

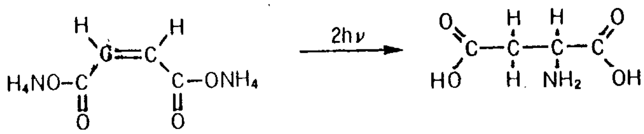
Vitamin D_3, a high-value added drug which is worth around Y3,000,000 per ton and has an annual production of around 20 tons in the world, is currently manufactured either by extraction from the liver oil of tuna or by a photochemical process involving exposure of 7-dehydro-cholesterol (7-DHC) to the mercury lamp. As can be seen from Figure3 , the yield depends on an efficient formation of P_3, the precursor of vitamin D_3; application of ultraviolet light from the mercury lamp, however, allows formation also of the other byproducts L_3 and T_3 and, these three substances being in equilibrium, the yield of the P_3 is limited to 35 percent. A stepwise irradiation with KrF-laser and N_2 laser in such a way that the formation of L_3 and T_3 be limited to a minimum and that L_3 and T_3 generated be converted to P_3, in contrast, afforded the vitamin D_3 eventually in as high a yield as 90 percent.

This process is of industrial significance in that it produced a high rate of conversion into an intended substance by means of an ingenious application of highly monochromic laser in accordance with differences in light absorption among individual constituents of the reaction mixture. A number of wavelength dependent reactions have so far been found wherein application of different wavelengths of laser results in different products from an identical substrate in photochemical reactions, which are of interest in terms of both basic and application sciences. The above example exhibits a wavelength effect in connection with an overall reaction system involving some intermediates, an effect which can be served also in a number of other photochemical reactions. The ultraviolet light from the conventional mercury lamp may be made monochromic by the use of filters, monochrometers, etc., but the intensity of the monochromic light thus produced goes down so far that an examination of the effect of the monochromic light is made nearly impossible. Laser beams, in contrast, afford a practical means to cope with the problem and have a widespread scope of applications.

In connection with the photochemical process of vitamin D, the effect of the width or duration of pulse waves thereon has also been investigated. Pulses of 4 picoseconds and 5 nanoseconds, each of the 4th harmonics of the Nd glass laser, were used for the irradiation of the above raw material such that the quantities of irradiation for both pulses are identical. The result has proved that the pulse of the shorter duration gives greater yield of P_3 since the longer pulse allows the P_3 formed to be subjected to further irradiation and hence to be turned into T_3. Lasers of shorter pulses, in general, are more effective in preventing a secondary reaction of the product.

3.4 Specific Laser Reaction Induced by High Levels of Excitation

Letokov, et al., have found that exposure of an aqueous solution of ammonium maleinate to Nd: YAG laser (226 nm, 30 ps, 2 mj) gives asparagic acid with a quantum yield of 0.4. Since the reaction involves a two-photon reaction and, hence, its maximum possible quantum yield is 0.5, the above result represents a high yield for the reaction. The success in the direct synthesis of an amino acid above is worthy of note also from the industrial viewpoint.



One example of the applications of photon of high energy and high luminescence, besides the above, is the direct synthesis of phenol from benzene way of an ionized state of the benzene by means of irradiation of a saturated aqueous solution of benzene with a collected beam of KrF-laser (2 j cm^{-2}). Another is formation of methylalcohol from methane and chlorine upon exposure of these gases that fill a vessel in the ratio of partial pressure of 100 to 20 (Torr) to a collected beam of F_2-laser, which leads to conversion of the methane into methyl radical and to subsequent reaction of the methyl radical with an oxygen atom in an excited state to give the product methyl alcohol. These reactions reported to date have only very low quantum yields, but pose long-term problems which promise development of important new reactions.

3.5 Pyrolytic Reactions

In the 1960s and 1970s, research on laser chemical reactions were limited largely to the vibration excitation state involving CO_2 laser, from which, however, the technology for the isotope enrichment has evolved and industrially significant pyrolytic reactions distinct from the ordinary pyrolytic ones have been discovered.

The feature of the laser pyrolytic reaction is its capacity for rapid heating and cooling and for eliminating the hot wall effect of the container by virtue of its orienting property. Furthermore, the method is available also for those materials having no capacity for infrared absorption by the addition of a sensitizing agent, SF_6 or SF_4, which absorbs laser beams and allows the pyrolytic reaction to take place in the homogenous system through transfer of energy.

In connection with the synthesis of tetrafluoroethylene, the raw material of fluorine resin, from pentafluoro-ethane, research was done on raising the selectivity for the intended product by exposure of the material to a collected beam of TEA CO_2-laser of 1,078.6 cm^{-1}. Upon raising the fluence from 2.7 j cm^{-1} to 17 j cm^{-1}, the selectivity went up from 9.6 to 32.7 percent.

$$CF_3CHF_2 \xrightarrow{\text{TEA } CO_2 \text{ laser}} CF_2=CF_2+CF_3CF_3$$
$$+CHF_3+CH_2F_2+CHF=CF_2+CHF_2CHF_2$$

In addition to the above, several research projects on halogenated hydrocarbons have been conducted.

Research is also underway on the manufacture of ethylene from ethanol, with high selectivity, by irradiation with 1,046.85 cm^{-1}-TEA-CO_2-laser.

$$CH_3CH_2OH \xrightarrow{\text{TEA } CO_2 \text{ laser}} CH_2=CH_2+H_2O+CH_4$$
$$+HC\equiv CH+CH_3CH_3+CO$$

A pyrolytic reaction in which a mixture of saturated, nonsaturated, and aromatic hydrocarbons with the sensitizing agent SF-6 admixed is irradiated with CO_2 lasers of pulse width 500 ns and 50 ns has been investigated and found to give higher yield than that of the conventional method for olefines or unsaturated hydrocarbons which are industrially of higher value

$$\begin{array}{c}\text{paraffin}+\\ \text{olefin}+\text{aromatic}\end{array} \xrightarrow[\text{Ar (5 Torr) } CO_2\text{laser}]{SF_6 \text{ (3 Torr) pulsed}} \begin{array}{l}CH_2=CH_2+CH_2\\ =CHCH_3+CH_4 \text{ etc.}\end{array}$$

3.6 Miscellaneous

Ishikawajima-Harima Heavy Industries and Nippon Zeon have jointly investigated technologies for extracting physiologically active, useful substances, e.g., amino acids, DNAs, and interferons from molds, bacteria, enzymes, etc. by means of lasers of wavelengths variable in the range 200 to 400 nonameters and developed a method for processing bacterial cells in which a particular bonding to cellular wall membrane is excited with the beam of a particular wavelength and useful substances liberated from the cell wall are extracted. The variable-wavelength laser is capable of coping with the multifarious properties of chemical substances and available for the investigation of the dependence of photochemical reaction on wavelength.

A method for the synthesis of optically active substances by means of the circular polarized light of high intensity and high quality produced by laser, the method of asymmetric synthesis, is also under investigation. The circular polarized light produced by Ar-ion laser is being investigated for the decomposition or conversion of one of an enantiomeric pair. Finally, laser chemical processes are promising as a chemical process for the thermally unstable, biological materials since the process allow rapid and selective photo-chemical process at low temperatures.

Possible Application of Laser in the Chemical Industry

Though a quarter of a century has passed since the discovery of the laser, its practical application in industrial chemical processes has yet to be seen. With the excessive hope once pinned on the reaction of selective combination having gone, the chemical industry has not been enthusiastic for the application of the laser. Under the circumstances a laser adapted to chemical application, excimer laser, made its appearance. The laser, if it is to be practicable, needs to display performances surpassing that of a photochemical process which has been made practicable in the nation and which involves the use of high output, long-life mercury lamps (60 kilowatt, 6,000 hours). As a technology for the control of chemical reaction, the laser, in comparison with stationary light, involves specificity in reaction and other superior features as a process and, hence, its practical application is ardently desired. Its eventual destiny, anyway, is dictated by its economic feasibility and credibility of the relevant equipment.

Table 2 shows an estimate ofn the number of laser machines necessary on the assumption of manufacture of bulk chemicals. The calculation was made also on the assumption of an operating rate of 70 percent for the machine which is equivalent to 6,000 hours per year. Requirements for the future excimer laser machines in relation to its pulse width, number of cycles, energy, etc. vary with the multiplicity of chemical reactions, but long life (for both machines and gases) and high performance must make the key to its availability in the chemical industry. The application of laser in the chemical industry is currently infrequent but potential needs for it are enormous and research on chemical synthesis, in particular, require various wavelengths of laser. The author is optimistic regarding the apparent bright future for the development of these machines.

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FUTURE OF NEW GLASS INDUSTRY EXAMINED

Tokyo NIKKO MATERIALS in Japanese Dec 86 pp 20-23

[Text] "New glass," which has emerged as the new material following new ceramics, is steadily making progress as the basic industry of the next generation. It is the glass material that has specific features in the manufacturing process differing from the conventional type, such as, to start with, optical fiber, photo mask, glass substrate, laser glass, optical memory, and bionic glass for dental roots. Each field in the industrial world has shown deep interest and is approaching the new glass from many different angles. The members of the New Glass Forum (NGF, representative agent Tetsuo Suzuki, president of Hoya Glass Co.), which was started in July last year, have been joined by about 90 companies consisting of all types of material industries such as the glass, metal, and chemical industries, and user industries such as electric-electronic equipment and precision apparatus. This is an example showing the "breadth" and promising prospects of this material. One of the aims of NGF is to assume international leadership in this rising industry, but whether the new glass really expands or not depends on how both usage and material develop in the future. We will look at the future of the industry, which seems at present to be the steadiest among other "trillion-yen industries" in the 21st century.

As an Apparatus of "New Civilization"

Categorizing various scientific techniques, research, and technical developments carried out individually in the fields of industries into a definite purpose or form and tailored as a scientific theme or an industrial field is considered to be a type of activity of civilization.

"New material" is exactly that. From ancient times, at the turning points of civilization, the materials of vessels and utensils have been changing. After various varieties of utensils such as stone, china, bronze, iron, and paper vessels and plastic were produced and basic materials were almost fully developed, new materials several times superior in quality emerged as a variation. This has become fundamental for the present society to advance as a high-level, information-oriented world.

New glass is nothing other than a new material to form a new civilization, as were fine ceramics and engineering plastics.

New glass has a variety of characteristics: 1) It allows light to pass through well; 2) it can efficiently dissolve many elements as a solid solvent and has variable features; 3) it is flexible; 4) it excels in durability, solidity, and resistance to chemicals; 5) it can treat surfaces; 6) it can denaturalize, such as crystallize and phase split; and 7) it is capable of minute small adjustments of various functions and features. The new glass displays these characteristics to a high level and at the same time represents "newness" in manufacturing methods.

The glass we have known is made by melting the raw material mixture at a temperature above 1,000°C and then cooling it to a solid state. Although this method, with the exception of progress in technique, has not changed since glassmaking started about 5,000 years ago, new glass has produced a glassmaking method with a totally new concept to widen the limit of the amorphous state of glass.

For example--

Zol gel method: Glass made by sintering the gel which comes from the hydrolysis of metal alcoholate and is adapted to make titanium type glass of zero expansion with the characteristics of low temperature formation of unmeltable glass.

Gaseous phase compound method: The process of making super purified glass by pyrolyzing gaseous materials such as tetrachloride silicon and tetrachloride germanium; applicable to quartz optic fiber.

Vaporizing method: The crystalline material is heated in a vacuum or vaporized by the application of an electron ray, then condensed on the basic board of low temperature. As a melting method it is suitable for making formed, nonamorphous thin glass membrane; applicable to optical memory and optic wave path.

Super-quick cooling method: The melted glass is cooled very quickly through the cooled roller. This, too, as a melting method can obtain formed nonamorphous glass and is applicable to supermagnetic glass.

Melting method without vessel: The glass is melted in a state of nongravity. It is suitable for making nonamorphous, formed, superpurified glass; applicable to infrared ray transmit metal oxide glass.

Atmospheric melting method: This method is used to make glass with fewer features by mixing a minute amount of oxide such as fluoride glass and chalcogenite glass.

As stated above, many new methods have already been developed. Other than these methods, there is glass crystallization by heat treatment, phase separation, and ion exchanging on the surface of glass. They represent the denaturation of glass by secondary process and are also the developing themes of new glass.

High Utilization of Various Characteristics

Several materials called new glass have appeared in the world under different circumstances such as developing material with specific features for a new use or planning a new use because of its distinctive feature. However, it is from now on that most of them will be put to practical use. The representative of NGF, Suzuki, considers that "the theme will take a good 10 years. I must say if the project blossoms by 2000, a good job will have been done."

The distinctive feature and functions of new glass can be divided roughly into four categories. They are the "optical feature," "electric magnet feature," "heat machinery feature," and "chemistry-bionic feature." The features and examples of its use are as follows.

Optical Feature

Ray transmittal--communication fiber, infrared optical fiber, microoptical lens; fluorescence--laser glass. Ray phase transmittal--glass for optical memory; selection permeability--thermic ray reflex glass, solar cell cover glass; sound and optic effect--ray modulate-polarize glass.

Electric Magnet Feature

Magnet optical effect--Faraday rotary glass; insulation--electroluminescence basic board, liquid crystal indication element basic board, solar cell basic board; ion conduction--super ion transmit glass.

Heat-Machinery Feature

Low inflation--zero inflate crystal glass; high strength--fiber strengthened crystal glass, auxinite light glass; manufacturing feature--machinable crystal glass.

Chemical-Bionic Feature

Corrosion resistance--glass for treating radioactive products, crystal glass for interior and exterior; adsorption--porous glass for the carrier of enzyme catalysis; agreeability to organism--glass for artificial bone, bionic dental root, and crystallized glass.

The history of new glass is said to have started in 1964 when the United States developed photochromix (transmissivity changes according to the strength of light). Thus, only a little over 20 years have passed. For this reason most of the uses given above are the first steps for practical research and are rather example uses for the future.

However, there are some, such as optical fiber, which have played an important role in the course of the transition of modern civilization. New glass has also played an active part, being used in compact disks and video disks. Let us look at some of the active examples.

Fostering the Optical Industry

Glass fiber, the leader of new glass, was invented in 1970. The foundation of optical technique was firmly built when the medium which can send light with little loss was developed. The needs of the community and the needs in techniques joined to promote rapid progress in optical techniques, and thus a new field called the "optical industry" was started as a new industry. The fields which adapt optical techniques are divided into fields related to information and to energy, but at the present time information utilization seems to be ahead. With the use of optical fiber, optical communication can produce new forms of communication such as data communication through digital signal and picture communication. Also, with the use of optical energy, the solar battery and laser process are promising in the future.

Due to the expanding uses and improvement of usage level, the quality and features of optical fiber need to be advanced further. Under these circumstances, the variety and methods of manufacture become quite numerous. Therefore, the variety of optical fibers can be classified from the material side into three types, quartz, multicomponents and the plastic type, and on the side of the refraction distribute plan into each form of step index, graded index (GI), and single mode (SM). [Sentence as published] Presently the fibers used for communication are mostly the quartz type, GI fiber, or SM fiber.

On the other hand, the methods of manufacture vary according to use and feature. Considering just the quartz type, there are many, such as MCVD (work from inside in gaseous phase), OVD (work from outside in gaseous phase), VAD network (work on an axis in gaseous phase), PCVD method (plasma activate CVD method), RT method, and PCF method (plastic classfiber method).

Also, multicomponents fiber (glass as core and plastic as clad), plastic fiber (directly connected continuous massive polymerization process of PMMA and spinning process), polarized wave surface optic fiber (can transmit information of phase and polarization as well as strength information), infrared ray transmit fiber (made with material whose limit of transmitted wavelength is stretched to long wave) are developed and put to practical use.

Incidentally, an optical fiber with less light loss, "super low light loss optical fiber," will be developed in the future. In the case of the quartz type, the light loss rate is quite low with the wavelength of the infrared light at 1.6 μ and 0.2 dB/km. Although these numbers are near the limit in terms of theory, considering the intercontinental super-long-distance optical communication of the future, it is necessary to lessen the loss of light.

One is fluoride fiber. Fluoride glass theoretically does not absorb light against infrared light of around 3 μ (wavelength). This is to say that it is a material that could become a "nonloss fiber." Also chalcogen fiber is being mentioned as a laser optical which could transmit energy.

The development of laser glass is different from that of the gas laser, such as the carbon dioxide and YAG lasers. Since it is a solid form laser there is the advantage that it can be enlarged. Thus, it has the possibility of promoting huge progress in the laser process field.

The IC leading modern industry, has the design structure of driving the electrical signal, but is promising in putting into practical use the "optical IC" which operates by light reflecting acceleration of data-processing speed. The structure is that of building an optical wave path on a basic board of nonoxide glass and accumulating optical circuit elements such as an optical detector, optical modulator, optical polarizer, and optical wave distributor. There is still a long way to go, but the subject is something to look forward to for the people concerned with new glass. In the same way it has great possibilities as the basic board for optical memory. In this field, although it has already been put to practical use for optical disks, it will be generalized more as a higher precision memory material as it has more stability against heat and moisture compared to the basic board of transparent plastics such as PMMA (methacrylate gum) and PC (polycarbonate).

Encountering Amorphous Metal

Apart from this, there are strong expectations for new glass as a biomaterial. Using it for the so-called artificial bones, dental roots, and tooth crowns, affinity to the organism is much superior and it is stronger compared to ceramics. Also concerning biotechnology, research is progressing to use porous glass as an enzyme carrier. The point is that it is more stable physically and chemically than the carrier of high molecule substances.

Thus, the use of new glass is unlimited, meaning that there are great hidden possibilities. However, mass production which has reached the industrial level, such as in optical fiber, is still few in number. It is an industry of the future, and the enterprises aiming for industrialization as future new glass companies are presently expanded into various industries.

Among them, the metal industry has shown extraordinary interest in this field. This is because there are many companies doing R&D on related material called amorphous metal, which is very similar to glass. There is hardly any boundary between new glass and amorphous metal on the molecule level. That is why the research on both materials is liable to make contact and the themes to criss-cross each other. Accordingly, it is unlikely that in the future people in charge of either material will carry on with no change. The glass companies of today will not necessarily be in charge of new glass in the future.

NGF representative Suzuki said: "New glass will eventually become a contest for various types of industries. It should not be limited just to the small field of the glass industry, but by competing with each other in the development of its use and material, it will grow as a real industry."

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